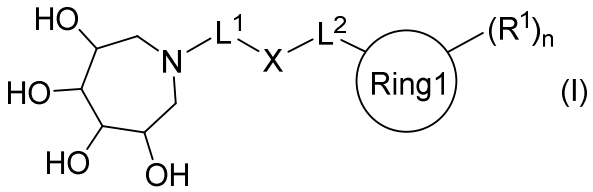
GBA1 and GCS dual modulator

[Field of the Invention]

[001] The present disclosure relates to a compound having GBA1 and GCS dual modulatory activity or a pharmaceutically acceptable salt thereof. Specifically, the present disclosure relates to a medicament containing a compound represented by formula (I), or a pharmaceutically acceptable salt thereof (hereinafter, the compound is referred to as a compound of the present disclosure):



(I)

[002] wherein all symbols represent the same meaning as the symbols described later.

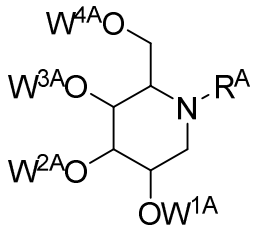
[Background Art]

[003] β-Glucocerebrosidase (GBA1) is an enzyme that hydrolyzes glucosylceramide, a glycolipid. Genetic mutations in GBA1 are known risk factors for the development of Gaucher disease, Parkinson's disease, and related synucleinopathies. In Gaucher disease, glucosylceramide accumulates in the liver, spleen, bone, and brain due to genetic mutations in GBA1, causing anemia, thrombocytopenia, hepatosplenomegaly, fracture, and serious neurological symptoms. Creation of pharmacological chaperones or gene therapy is considered to be effective as a therapeutic strategy for Gaucher disease (Non-patent document 1).

[004] Glucosylceramide is known to be synthesized by glucosylceramide synthase (GCS), and inhibition of GCS may affect the progression of synucleinopathy by reducing glucosylceramide levels (Non-patent document 2). Therefore, compounds that regulate GBA1 and GCS may be useful in the treatment of Gaucher disease, Parkinson's disease, and related synucleinopathies.

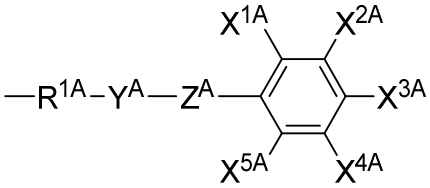
[005] On the other hand, Patent Document 1 states that the compound represented by the following formula (A) is a compound having ceramide glucosyltransferase inhibition, β-glucocerebrosidase inhibition, and β-glucocerebrosidase chaperone activity.

[006] Formula (A) is as follows:



(A)

[007] wherein R^A is:



[008] R^{1A} is a substituted or unsubstituted alkyl group;

[009] W^{1A-4A} are independently selected from hydrogen, substituted or unsubstituted alkyl groups, substituted or unsubstituted haloalkyl groups, substituted or unsubstituted alkanoyl groups, substituted or unsubstituted aroyl groups, or substituted or unsubstituted haloalkanoyl groups;

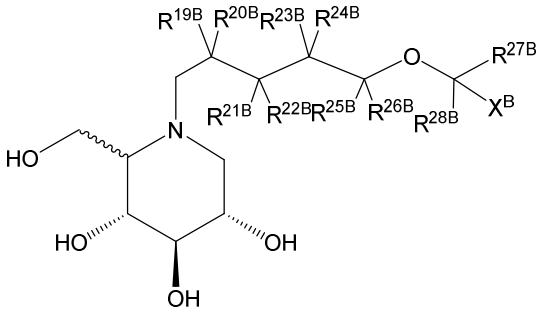
[010] X^{1A-5A} are independently selected from H, NO_2, N_3, or NH_2;

[011] Y^A is absent or is a substituted or unsubstituted C1-alkyl group, other than carbonyl; and

[012] Z^A is selected from a bond or NH, and the definition of groups was partially excerpted.

[013] Patent Document 2 states that the compound represented by the following formula (B) is a compound having an increased inhibitory potency towards GCS, and/or an increased inhibitory potency towards GBA2, and/or a decreased inhibitory potency towards GBA1.

[014] Formula (B) is as follows:



(B)

[015] wherein each of R^{19B}-R^{26B} is independently selected from H, F, Me or Et;

[016] R^{27B} and R^{28B} is independently selected from the group consisting of H, F, CF_3 and C1-C8 linear or branched alkyl;

[017] X^B is 5-6 membered cyclic group substituted by 5-6 membered cyclic group, and the definition of groups was partially excerpted.

[Prior Art Documents]

[018] [Patent Documents]

[019] [Patent Document 1] WO2014/179438

[020] [Patent Document 2] WO2015/147639

[021] [Non-Patent Documents]

[022] [Non-Patent Document 1] Molecular Neurodegeneration (2019) 14:36

[023] [Non-Patent Document 2] Neurobiology of Disease 159 (2021)105507

[Summary of the Invention]

[Problems to be Solved by the Invention]

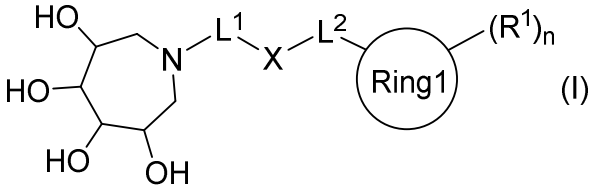
[024] An object of the present invention is to provide a compound having GBA1 and GCS dual modulatory activity.

[025] [Means for Solving the Problems]

[026] As a result of intensive studies to solve the above problems, the present inventors have found that a compound represented by formula (I) described later has potent GBA1 and GCS dual modulatory activity.

[027] That is, one aspect of the present disclosure provides the following embodiments and the like.

[028] [A] A compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[029] wherein

[030] L^1 represents (1) a C4-7 alkylene, (2) a C4-7 alkenylene, or (3) a C4-7 alkynylene,

[031] L^1 may be substituted with one to five R^{L1}s,

[032] R^{L1} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6

haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, or (10) a hydroxyl group,

[033] a plurality of R^{L1}s may be the same or different,

[034] L^2 represents (1) a C1-3 alkylene, (2) a C2-3 alkenylene or (3) a C2-3 alkynylene,

[035] L^2 may be substituted with one to four R^{L2}s,

[036] R^{L2} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, or (10) a hydroxyl group,

[037] a plurality of R^{L2}s may be the same or different,

[038] X represents (1) a bond, (2) -O-, (3) -S-, (4) -SO-, or (5) $-SO_2-$,

[039] Ring 1 represents (1) a benzene ring (2) a naphthalene ring or (3) a 5- to 10-membered heterocyclyl,

[040] R^1 represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, (10) a C5-7 carbocyclyl, (11) a 5- to 7-membered heterocyclyl, (12) -O-(C5-7 carbocyclyl), or (13) -O-(5- to 7-membered heterocyclyl),

[041] a plurality of R^1s may be the same or different,

[042] the groups (2) to (13) in R^1 may be substituted with one to five R^{1-1}s,

[043] R^{1-1} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, (10) a C1-6 alkyl sulfonyl group, (11) a cyano group, or (12) a phenyl group,

[044] a plurality of R^{1-1}s may be the same or different,

[045] the symbol:



[046] represents that a substituent is bonded to the α-configuration, β-configuration or a mixture of α- and β-configurations at an appropriate ratio, and

[047] n represents an integer of 0 to 5.

[048] [B] A pharmaceutical composition comprising a compound according to the above [A] or a pharmaceutically acceptable salt thereof as an active ingredient, and a pharmaceutically acceptable carrier.

[049] [C] The pharmaceutical composition according to the above [B], which is a GBA1 chaperone modulator.

[050] [D] The pharmaceutical composition according to the above [B], which is a GCS inhibitor.

[Effects of the Invention]

[051] The compound of the present disclosure has GBA1 and GCS dual modulatory activity, and thus the compound of the present disclosure is useful as an agent for preventing and/or treating a disease associated with GBA1 and/or GCS.

[Embodiments for Carrying Out the Invention]

[052] Hereinafter, the present disclosure will be described in detail.

[053] In the present specification, GBA1 and GCS dual modulatory activity means both GBA1 chaperon activity and GCS inhibitory activity.

[054] In the present specification, examples of the halogen atom include fluorine, chlorine, bromine, and iodine atoms.

[055] In the present specification, examples of the C1-6 alkyl group include linear or branched methyl, ethyl, propyl, butyl, pentyl, hexyl groups, and isomers thereof.

[056] In the present specification, examples of the C2-6 alkenyl group include linear or branched ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl groups, and isomers thereof.

[057] In the present specification, examples of the C2-6 alkynyl group include linear or branched ethynyl, propynyl, butynyl, butadiynyl, pentynyl, pentadiynyl, hexynyl, hexadiynyl groups, and isomers thereof.

[058] In the present specification, examples of the C1-3 alkylene include methylene, ethylene, propylene, and isomers thereof.

[059] In the present specification, examples of the C2-3 alkenylene include linear or branched vinylene, propenylene, and isomers thereof.

[060] In the present specification, examples of the C2-3 alkynylene include linear or branched ethynylene, propynylene, and isomers thereof.

[061] In the present specification, examples of the C3-6 alkylene include linear or branched propylene, butylene, pentylene, hexylene, and isomers thereof.

[062] In the present specification, examples of the C3-6 alkenylene include linear or branched propenylene, butenylene, pentenylene, hexenylene, and isomers thereof.

[063] In the present specification, examples of the C3-6 alkynylene include linear or branched propynylene, butynylene, pentynylene, hexynylene, and isomers thereof.

[064] In the present specification, examples of the C4-7 alkylene include linear or branched butylene, pentylene, hexylene, heptylene, and isomers thereof.

[065] In the present specification, examples of the C4-7 alkenylene include linear or branched butenylene, pentenylene, hexenylene, heptenylene, and isomers thereof.

[066] In the present specification, examples of the C4-7 alkynylene include linear or branched butynylene, pentynylene, hexynylene, heptynylene, and isomers thereof.

[067] In the present specification, the C1-6 haloalkyl group means, for example, a linear or branched alkyl group substituted with one or more halogen atoms. Specific examples of the C1-6 haloalkyl group include a fluoromethyl group, a chloromethyl group, a bromomethyl group, an iodomethyl group, a difluoromethyl group, a trifluoromethyl group, a 1-fluoroethyl group, a 2-fluoroethyl group, a 2-chloroethyl group, a pentafluoroethyl group, a 1-fluoropropyl group, a 2-chloropropyl group, a 3-fluoropropyl group, a 3-chloropropyl group, a 4,4,4-trifluorobutyl group, a 4-bromobutyl group, a 5,5,5-trifluoropentyl group, a 6,6,6-trifluorohexyl group, and isomers thereof.

[068] In the present specification, the C2-6 haloalkenyl group means, for example, a linear or branched alkenyl group substituted with one or more halogen atoms. Specific examples of the C2-6 haloalkenyl group include a 1-fluoroethenyl group, a 2-fluoroethenyl group, a 2-chloroethenyl group, a 1-fluoropropenyl group, a 2-chloropropenyl group, a 3-fluoropropenyl group, a 3-chloropropenyl group, a 4-bromobutenyl group, a 5,5,5-trifluoropentenyl group, a 6,6,6-trifluorohexenyl group, and isomers thereof.

[069] In the present specification, the C2-6 haloalkynyl group means, for example, a linear or branched alkynyl group substituted with one or more halogen atoms. Specific examples of the C2-6 haloalkynyl group include a 2-fluoroethynyl group, a 2-chloroethynyl group, a 3-fluoropropynyl group, a 3-chloropropynyl group, a 4-bromobutynyl group, a 5,5,5-trifluoropentynyl group, a 6,6,6-trifluorohexynyl group, and isomers thereof.

[070] In the present specification, examples of the C1-6 alkoxy group includes linear or branched methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy groups, and isomers thereof.

[071] In the present specification, the C1-6 haloalkoxy group means, for example, a linear or branched alkoxy group substituted with one or more halogen atoms. Specific examples of

the C1-6 haloalkoxy group include a fluoromethoxy group, a chloromethoxy group, a bromomethoxy group, an iodomethoxy group, a difluoromethoxy group, a trifluoromethoxy group, a 1-fluoroethoxy group, a 2-fluoroethoxy group, a 2-chloroethoxy group, a pentafluoroethoxy group, a 1-fluoropropoxy group, a 2-fluoropropoxy group, a 2-chloropropoxy group, a 3-fluoropropoxy group, a 3-chloropropoxy group, a 4,4,4-trifluorobutoxy group, a 4-bromobutoxy group, a 5,5,5-trifluoropentyloxy group, a 6,6,6-trifluorohexyloxy group, and isomers thereof.

[072] In the present specification, examples of the C5-7 carbocyclyl include cyclopentane, cyclohexane, cycloheptane, cyclopentene, cyclohexene, cycloheptene, cyclopentadiene, cyclohexadiene, cycloheptadiene, and benzene rings.

[073] In the present specification, examples of the 5- to 7-membered heterocyclyl include pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, pyran, thiophene, thiopyran, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, thiadiazole, thiazine, thiadiazine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxadiazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, dithiane, azepine, diazepine, oxepin, thiepin, oxazepine, oxadiazepine, thiazepine, thiadiazepine, dihydroazepine, tetrahydroazepine, perhydroazepine, dihydrodiazepine, tetrahydrodiazepine, perhydrodiazepine, dihydrooxepin, tetrahydrooxepin, perhydrooxepin, dihydrothiepin, tetrahydrothiepin, perhydrothiepin, dihydrooxazepine, tetrahydrooxazepine, perhydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, perhydrooxadiazepine,

dihydrothiazepine, tetrahydrothiazepine, perhydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, and perhydrothiadiazepine rings.

[074] In the present specification, examples of the 5- to 10-membered heterocyclyl include the 5- to 7-membered heterocyclyl, and indole, isoindole, indolizine, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, dithianaphthalene, indazole, quinoline, isoquinoline, quinolizine, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzimidazole, chromene, benzofurazan, benzothiadiazole, benzotriazole, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorpholine, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, dioxaindane, benzodioxane, chroman, benzodithiolane, benzodithiane, azaspiro[4.4]nonane, oxazaspiro[4.4]nonane, dioxaspiro[4.4]nonane, azaspiro[4.5]decane, thiaspiro[4.5]decane, dithiaspiro[4.5]decane, dioxaspiro[4.5]decane, oxazaspiro[4.5]decane, azabicyclo[3.2.1]octane, oxabicyclo[3.2.1]octane, thieno[3,2-c]pyrazole, thieno[2,3-c]pyrazole, thieno[2,3-d]thiazole, thieno[2,3-d][1.2.3]triazole, dihydropyrano[3,4-d]thiazole, dihydrothieno[2,3-b]pyran, dihydrothieno[3,2-c]pyran, dihydrothieno[3,2-b]pyran, dihydrothieno[3,2-c]thiopyran, tetrahydrothieno[3,2-b]pyridine, tetrahydrothieno[3,2-c]pyridine, and thieno[3,2-c]pyridine rings.

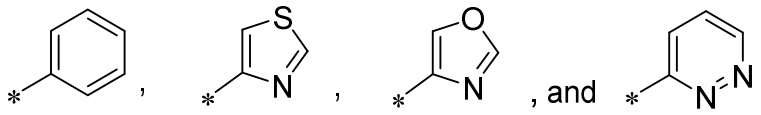
[075] In the present disclosure, L^1 is preferably a C4-7 alkylene group, and more preferably a hexylene group.

[076] In the present disclosure, L^2 is preferably a methylene.

[077] In the present disclosure, X is preferably -O- or -S-, and more preferably -O-.

[078] In the present disclosure, Ring 1 is preferably a benzene ring or a 5- to 7-membered heterocyclyl, and more preferably a benzene ring, a thiazole ring, an oxazole ring or

pyridazine ring, and still more preferably a ring structure selected from the group consisting of:



[079] wherein the * mark represents a bonding position with L^2.

[080] In the present disclosure, R^1 is preferably a halogen atom, a C1-6 alkyl group, a C2-6 alkenyl group, a C1-6 alkoxy group, a benzene ring or a 5- to 6-membered heterocyclic ring, and more preferably a halogen atom, a C1-6 alkyl group, a C1-6 alkoxy group, or a benzene ring, and still more preferably a C1-6 alkyl group, or a benzene ring.

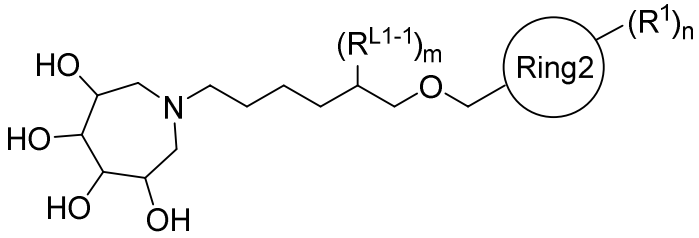
[081] In the present disclosure, R^{L1} is preferably a halogen atom, and more preferably a fluorine atom.

[082] In the present disclosure, R^{L2} is preferably a halogen atom, a C1-6 alkyl group, and more preferably a methyl group.

[083] In the present disclosure, R^{1-1} is preferably a halogen atom, a C1-6 alkyl group, a C1-6 alkoxy group, a C1-6 haloalkyl group, or a C1-6 haloalkoxy group, and more preferably a halogen atom, a methyl group, or a methoxy group.

[084] In the present disclosure, n is preferably 0, 1, or 2.

[085] In the present disclosure, the compound represented by formula (I) is preferably a compound represented by formula (I-1):

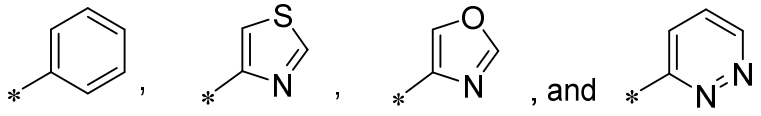


(I-1)

[086] wherein R^{L1-1} represents (1) a halogen atom, or (2) a C1-6 alkyl group,

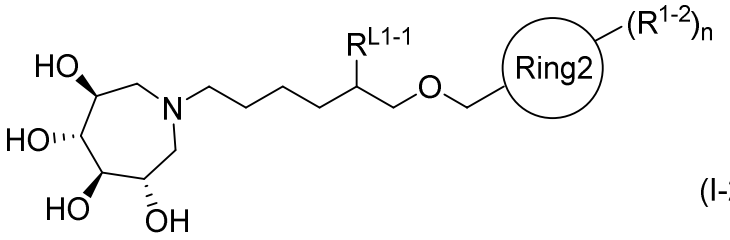
[087] m represents an integer of 1 to 2,

[088] Ring 2 represents a ring structure selected from the group consisting of the following ring structures;



[089] wherein the * mark represents a bonding position with methylene, and

[090] other symbols represent the same meaning as the above symbols, and more preferably a compound represented by formula (I-2):



(I-2)

[091] wherein R^{1-2} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C1-6 alkoxy group, or (4) a phenyl group, the groups (2) to (4) in R^{1-2} may be substituted with one to five R^{1-1}s, and other symbols represent the same meaning as the above symbols.

[092] In the present disclosure, the compound represented by formula (I) is preferably a combination of the preferred definitions of L^1, L^2, X, Ring 1, R^1, R^{L1}, R^{L2}, R^{1-1}, and n.

[093] In the present disclosure, the compound represented by formula (I-1) is preferably a combination of the preferred definitions of Ring 2, R^1, R^{L1-1}, R^{1-1}, m, and n.

[094] In the present disclosure, the compound represented by formula (I-2) is preferably a combination of the preferred definitions of Ring 2, R^{1-2}, R^{L1-1}, R^{1-1}, and n.

[095] In the present disclosure, another embodiment of the compound represented by formula (I) is most preferably an example compound described in Examples described later or a pharmaceutically acceptable salt thereof.

[096] All isomers are included in the present disclosure unless otherwise indicated. For example, the alkyl group, the alkoxy group, the alkylene group, and the like include linear groups and branched groups thereof. In addition, isomers (E-, Z-, cis-, and trans-forms) in a double bond, a ring, and a fused ring, isomers (R-, S-forms, α-, β-forms, enantiomer, and diastereomer) due to the presence of an asymmetric carbon, optically active substances (D-, L-, d-, and l-forms) having optical rotation, polar substances obtained through chromatographic separation (high-polarity substances and low-polarity substances), equilibrium compounds, rotational isomers, mixtures of these at an appropriate ratio, and racemic mixtures are all included in the present disclosure. In addition, all isomers by tautomerism are also included in the present disclosure.

[097] In the present disclosure, unless otherwise specified, the symbol:



[098] represents that a substituent is bonded to the back side of the paper surface (that is, α-configuration), the symbol:



[099] represents that a substituent is bonded to the front side of the paper surface (that is, β-configuration), and the symbol binding to chiral carbon atom:



[0100] represents that a substituent is bonded to the α-configuration, β-configuration or a mixture of α- and β-configurations at an appropriate ratio, as would be apparent to those skilled in the art.

[Salt]

[0101] The compound represented by formula (I) is converted into a salt by a known method.

[0102] The salt is a pharmaceutically acceptable salt.

[0103] The salt is preferably water-soluble.

[0104] Examples of the pharmaceutically acceptable salt include, acid addition salts, alkali metal salts, alkaline earth metal salts, ammonium salts, and amine salts.

[0105] Examples of the acid addition salt include inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, and nitrate, or organic acid salts such as acetate, lactate, tartrate, benzoate, citrate, methanesulfonate, ethanesulfonate, trifluoroacetate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, and gluconate.

[0106] Examples of the alkali metal salt include a potassium salt and a sodium salt.

[0107] Examples of the alkaline earth metal salt include a calcium salt and a magnesium salt.

[0108] Examples of the ammonium salt include a tetramethylammonium salt.

[0109] Examples of the amine salt include a triethylamine salt, a methylamine salt, a dimethylamine salt, a cyclopentylamine salt, a benzylamine salt, a phenethylamine salt, a piperidine salt, a monoethanolamine salt, a diethanolamine salt, a tris(hydroxymethyl)aminomethane salt, a lysine salt, an arginine salt, and an N-methyl-D-glucamine salt.

[0110] In addition, the compound of the present disclosure can be converted into an N-oxide by any method. The N-oxide represents a compound obtained by oxidizing a nitrogen atom of the compound represented by formula (I).

[0111] The compound represented by formula (I) and a pharmaceutically acceptable salt thereof may exist in a non-solvated form or in a solvated form with a pharmaceutically

acceptable solvent such as water or ethanol. The solvate is preferably a hydrate. The compound represented by formula (I) and a pharmaceutically acceptable salt thereof can be converted into a solvate.

[0112] The compound represented by formula (I) can form a cocrystal with an appropriate cocrystal former. The cocrystal is preferably a pharmaceutically acceptable cocrystal that is formed with a pharmaceutically acceptable cocrystal former. The cocrystal is typically defined as a crystal in which two or more different molecules are formed by intermolecular interaction that is different from ionic bonds. The cocrystal may be a complex of a neutral molecule and a salt. The cocrystal can be prepared by a known method, for example, by melting crystallization, recrystallization from a solvent, or physically pulverizing the components together. Suitable cocrystal formers include those described in WO 2006/007448.

[0113] In the present disclosure, all references to the compound of the present disclosure include a compound represented by formula (I), a pharmaceutically acceptable salt thereof, an N-oxide thereof, a solvate thereof (for example, a hydrate), or a cocrystal thereof, or an N-oxide of a pharmaceutically acceptable salt of the compound represented by formula (I), a solvate thereof (for example, a hydrate), or a cocrystal thereof.

[Prodrug]

[0114] The prodrug of the compound represented by formula (I) refers to a compound that is converted into the compound represented by formula (I) through a reaction with an enzyme, gastric acid, or the like in vivo. Examples of the prodrug of the compound represented by formula (I) include: compounds in which an amino group is acylated, alkylated, or phosphorylated (for example, compounds in which the amino group of the compound represented by formula (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidyl methylated, pivaloyloxymethylated, acetoxymethylated, tert-butylated, or the like) in the case where the compound represented by formula (I) has an amino group; compounds in which a hydroxyl group is acylated, alkylated, phosphorylated, or borated (for example, compounds in which the hydroxyl group of the compound represented by formula (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated, or the like) in the case where the compound represented by formula (I) has a hydroxyl group; and compounds in which a carboxy group is esterified or

amidated (for example, compounds in which the carboxy group of the compound represented by formula (I) is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, 1-{(ethoxycarbonyl)oxy}ethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, 1-{[(cyclohexyloxy)carbonyl]oxy}ethyl esterified, methylamidated, or the like) in the case where the compound represented by formula (I) has a carboxy group. These compounds can be produced by a method known per se. The prodrug of the compound represented by formula (I) may be either a hydrate or a non-hydrate. In addition, the prodrug of the compound represented by formula (I) may be a compound that is converted into the compound represented by formula (I) under a physiological condition as described in "Development of Pharmaceuticals", Vol. 7, "Molecular Design", pp. 163 to 198, published by Hirokawa Shoten, 1990.

[0115] Furthermore, each atom constituting the compound represented by formula (I) may be substituted with an isotope thereof (for example, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{16}N, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{77}Br, and ^{125}I) or the like.

[Method for producing compound of present disclosure]

[0116] The compound of the present disclosure can be produced by appropriately improving known methods, for example, methods shown below, methods equivalents thereto, the method described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 3rd Edition (Richard C. Larock, John Wiley & Sons Inc, 2018), the methods described in Examples or the like, and using a combination thereof. A salt may be used as the starting material thereof. The order of carrying out each reaction can be appropriately changed depending on the protecting group introduced and reaction conditions.

[0117] In addition, a compound having an amino group, a carboxyl group, or a hydroxyl group can be produced, if necessary, by performing a known deprotection reaction after an appropriate reaction step, by using a compound protected with a protecting group commonly used for these groups. The protecting group is, for example, the protecting groups described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 5th Edition, 2014.

[0118] Examples of the protecting group of a carboxyl group include methyl, ethyl, tert-butyl, trichloroethyl, benzyl (Bn), phenacyl, p-methoxybenzyl, trityl, and 2-chlorotrityl.

[0119] Examples of the protecting group of an amino group or a tetrazolyl group include a benzyloxycarbonyl group, a tert-butoxycarbonyl group, an allyloxycarbonyl (Alloc) group, a

1-methyl-1(4-biphenyl)ethoxycarbonyl (Bpoc) group, a trifluoroacetyl group, a 9-fluorenylmethoxycarbonyl group, a benzyl (Bn) group, a p-methoxybenzyl group, a benzyloxymethyl (BOM) group, and a 2-(trimethylsilyl)ethoxymethyl (SEM) group.

[0120] Examples of the protecting group of a hydroxyl group or hydroxamic acid include methyl, trityl, methoxymethyl (MOM), 1-ethoxyethyl (EE), methoxyethoxymethyl (MEM), 2-tetrahydropyranyl (THP), trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), acetyl (Ac), pivaloyl, benzoyl, benzyl (Bn), p-methoxybenzyl, allyloxycarbonyl (Alloc), and 2,2,2-trichloroethoxycarbonyl (Troc).

[0121] The deprotection reaction is known, and can be performed by, for example, the following methods: (1) a deprotection reaction by alkaline hydrolysis;

[0122] (2) a deprotection reaction under an acidic condition;

[0123] (3) a deprotection reaction by hydrogenolysis;

[0124] (4) a deprotection reaction of a silyl group;

[0125] (5) a deprotection reaction by using a metal; and

[0126] (6) a deprotection reaction by using a metal complex.

[0127] These methods are specifically described as follows.

(1) The deprotection reaction by alkaline hydrolysis is performed, for example, at 0 to 40℃, in an organic solvent (for example, methanol, tetrahydrofuran (hereinafter, THF), and dioxane), by using a hydroxide of an alkali metal (for example, sodium hydroxide, potassium hydroxide, and lithium hydroxide), a hydroxide of an alkaline earth metal (for example, barium hydroxide and calcium hydroxide), a carbonate (for example, sodium carbonate and potassium carbonate), or an aqueous solution or mixture thereof.

(2) The deprotection reaction under an acidic condition is performed, for example, at 0 to 100℃, in an organic solvent (for example, dichloromethane, chloroform, dioxane, ethyl acetate, methanol, isopropyl alcohol, THF, and anisole), in an organic acid (for example, acetic acid, trifluoroacetic acid, methanesulfonic acid, and p-tosylic acid) or an inorganic acid (for example, hydrochloric acid and sulfuric acid), or a mixture thereof (for example, hydrogen bromide/acetic acid), in the presence or absence of 2,2,2-trifluoroethanol.

(3) The deprotection reaction by hydrogenolysis is performed, for example, at 0 to 200℃, in a solvent (for example, an ether-based solvent such as THF, dioxane, dimethoxyethane, and diethyl ether; an alcohol-based solvent such as methanol and ethanol; a benzene-based solvent such as benzene and toluene; a ketone-based solvent such as acetone and methyl ethyl ketone; a nitrile-based solvent such as acetonitrile; an amide-based solvent

such as N,N-dimethylformamide (hereinafter, DMF); water, ethyl acetate, acetic acid, or a mixed solvent of two or more thereof), in the presence of a catalyst (for example, palladium-carbon, palladium black, palladium hydroxide-carbon, platinum oxide, and Raney nickel), under a hydrogen atmosphere under normal pressure or pressure, or in the presence of ammonium formate.

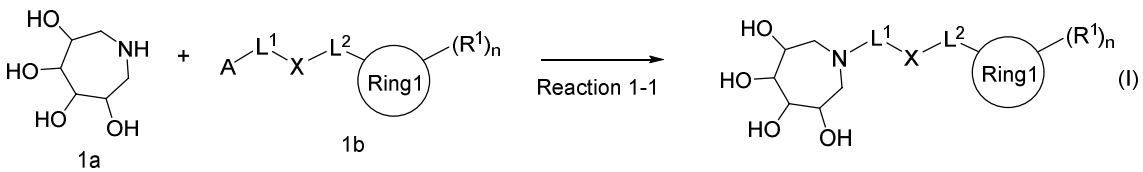
(4) The deprotection reaction of a silyl group is performed, for example, at 0 to 40℃, in an organic solvent (for example, THF and acetonitrile) miscible with water, by using tetrabutylammonium fluoride. In addition, the deprotection reaction is performed, for example, at -10 to 100℃, in an organic acid (for example, acetic acid, trifluoroacetic acid, methanesulfonic acid, and p-tosylic acid) or an inorganic acid (for example, hydrochloric acid and sulfuric acid), or a mixture thereof (for example, hydrogen bromide/acetic acid).

(5) The deprotection reaction using a metal is performed, for example, at 0 to 40℃, in an acidic solvent (for example, a mixed solution of acetic acid, a buffer solution having a pH of 4.2 to 7.2, or a solution thereof with an organic solvent such as THF), in the presence of powdery zinc while applying ultrasonic waves if necessary.

(6) The deprotection reaction using a metal complex is performed, for example, at 0 to 40℃, in an organic solvent (for example, dichloromethane, DMF, THF, ethyl acetate, acetonitrile, dioxane, and ethanol), water, or a mixed solvent thereof, in the presence of a trapping reagent (for example, tributyltin hydride, triethylsilane, dimedone, morpholine, diethylamine, and pyrrolidine), an organic acid (for example, acetic acid, formic acid, and 2-ethylhexanoic acid), and/or an organic acid salt (for example, sodium 2-ethylhexanoate and potassium 2-ethylhexanoate), in the presence or absence of a phosphine-based reagent (for example, triphenylphosphine), by using a metal complex (for example, tetrakistriphenylphosphine palladium(0), bis(triphenylphosphine)palladium(II) dichloride, palladium(II) acetate, and tris(triphenylphosphine)rhodium(I) chloride).

[0128] The compound represented by formula (I) can be produced by Reaction Scheme 1.

Reaction Scheme 1

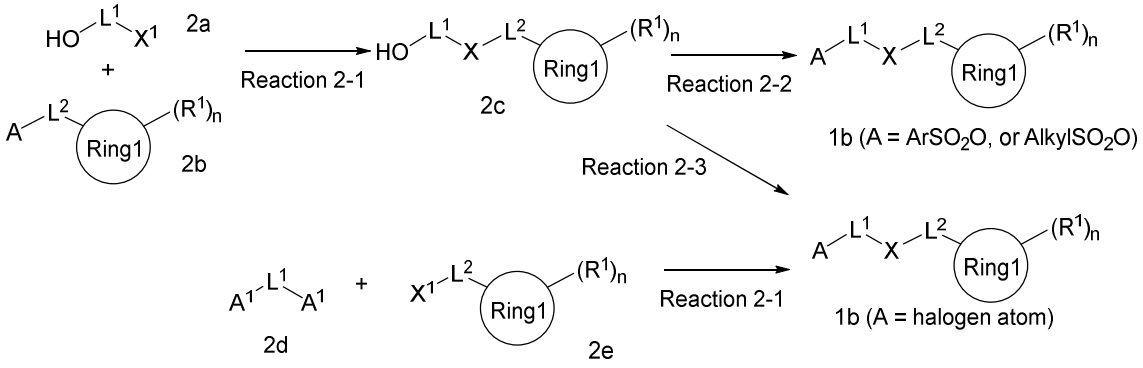


[0129] Wherein A represents a leaving group (for example, halogen atom, aryl sulfonate or alkyl sulfonate), and other symbols represent the same meaning as described above.

[0130] In Reaction Scheme 1, Reaction 1-1 is an alkylation reaction of amino group. The alkylation reaction of amino group is known, and is performed, for example, through reaction at 0 to 200°C, in an organic solvent (DMF, dimethyl sulfoxide, chloroform, dichloromethane, diethyl ether, THF, methyl t-butyl ether, and the like), in the presence of a base (triethylamine, diisopropylethylamine, sodium carbonate, sodium bicarbonate, potassium carbonate, cesium carbonate, tripotassium phosphate, cesium fluoride, barium hydroxide, tetrabutylammonium fluoride, and the like), in the presence of an inorganic salts (potassium iodide) or an aqueous solution or mixture thereof.

[0131] The compound represented by formula (1b) can be produced by Reaction Scheme 2.

Reaction Scheme 2



[0132] Wherein X^1 represents OH or SH, A^1 represents halogen atom, and other symbols represent the same meaning as described above.

[0133] In Reaction Scheme 2, Reaction 2-1 is an alkylation reaction of hydroxyl group or thiol group. The alkylation reaction of hydroxyl group is known, and is performed, for example, through reaction at 0 to 200°C, in an organic solvent (DMF, dimethyl sulfoxide, chloroform, dichloromethane, diethyl ether, THF, methyl t-butyl ether, and the like), in the presence of a base (triethylamine, diisopropylethylamine, sodium carbonate, sodium bicarbonate, potassium carbonate, cesium carbonate, tripotassium phosphate, cesium fluoride, barium hydroxide, tetrabutylammonium fluoride, potassium t-butoxide, sodium hydride and the like), in the presence of an inorganic salts (potassium iodide) in the presence of a phase transfer catalyst (tetrabutylammonium bromide, tetrabutylammonium iodide and the like) or an aqueous solution or mixture thereof.

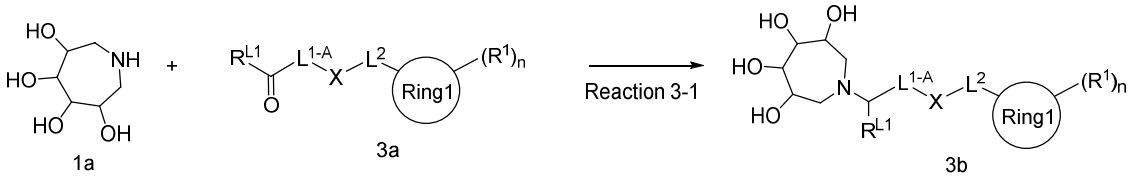
[0134] In Reaction Scheme 2, Reaction 2-2 is a sulfonylation reaction of hydroxyl group. The sulfonylation reaction of hydroxyl group is known, and is performed, for example, through reaction at 0 to 100°C, in an organic solvent (acetonitrile, chloroform, dichloromethane, pyridine, and the like), in the presence of a sulfonylation agent (p-

toluenesulfonyl chloride, methanesulfonyl chloride, methanesulfonic anhydride and lithium bromide and the like), in the presence or absence of a base (triethylamine, diisopropylethylamine, sodium carbonate, sodium bicarbonate, potassium carbonate and the like) or an aqueous solution or mixture thereof.

[0135] In Reaction Scheme 2, Reaction 2-3 is a halogenation reaction of hydroxyl group. The halogenation reaction of hydroxyl group is known, and is performed, for example, through reaction at 0 to 100°C, in an organic solvent (THF, toluene, chloroform, dichloromethane, pyridine and the like), in the presence of a halogenation agent (carbon tetrabromide, triphenylphosphine, phosphorous tribromide, methanesulfonic anhydride lithium bromide and the like), in the presence of a base (triethylamine, diisopropylethylamine, sodium carbonate, sodium bicarbonate, potassium carbonate and the like) or an aqueous solution or mixture thereof.

[0136] The compound represented by formula (3b) can be produced by Reaction Scheme 3.

Reaction Scheme 3

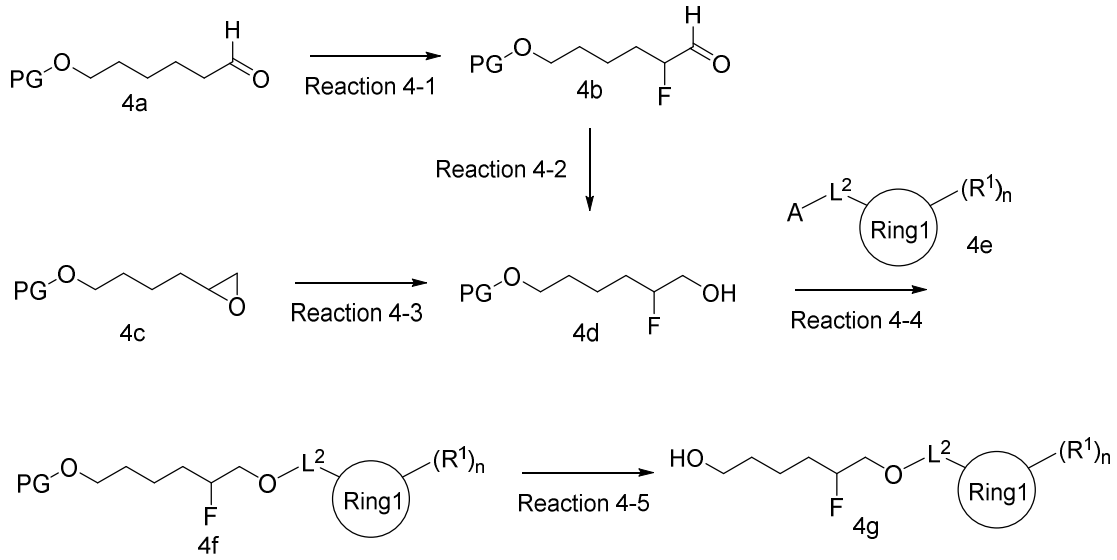


[0137] Wherein L^{1-A} represents (1) a C3-6 alkylene, (2) a C3-6 alkenylene, or (3) a C3-6 alkynylene, and other symbols represent the same meaning as described above.

[0138] In Reaction Scheme 3, Reaction 3-1 is a reductive amination. The reductive amination is known, and is performed, for example, through reaction at a temperature of 0 to 40°C in an organic solvent (e.g., dichloroethane, dichloromethane, dimethylformamide, acetic acid, and a mixture thereof) in the presence of a reducing agent (e.g., sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride).

[0139] In one aspect, a compound corresponding to the compound represented by formula (4g) can be produced by Reaction Scheme 4.

Reaction Scheme 4



[0140] Wherein PG represents a protecting group, and other symbols represent the same meaning as described above.

[0141] In Reaction Scheme 4, Reaction 4-1 is a fluorination reaction. The fluorination reaction is known, and is performed, for example, through reaction at a temperature of -20 to 40℃, in an organic solvent (e.g., THF, acetonitrile, EtOAc, chloroform, isopropyl alcohol and a mixture thereof), in the presence of hydrogen fluoride salts (e.g. triethylamine tris(hydrogen fluoride), pyridine hydrogen fluoride, potassium hydrogen bifluoride and the like) , in the presence of organic catalyst (DL-proline, L-proline, D-proline, (5R)-(+)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid, (5S)-(+)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid and the like).

[0142] In Reaction Scheme 4, Reaction 4-2 is a reduction reaction of an aldehyde group, and is performed at 0 to 40℃, in an organic solvent (dichloroethane, dichloromethane, DMF, THF, a mixture thereof, and the like), in the presence of a reducing agent (such as sodium borohydride).

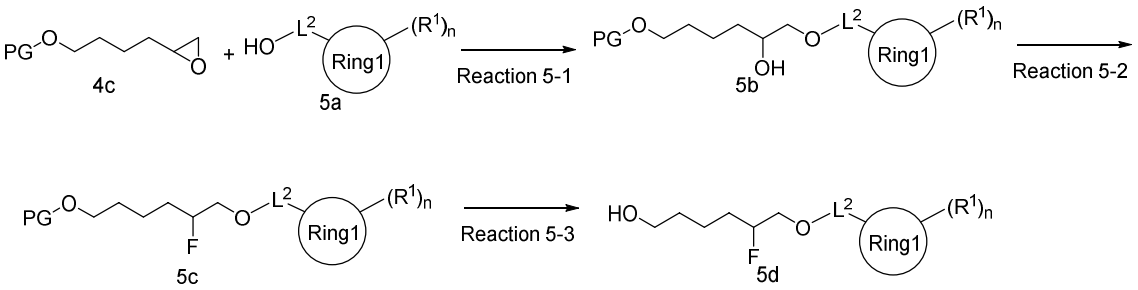
[0143] In Reaction Scheme 4, Reaction 4-3 is a fluorination reaction. The fluorination reaction is known, and is performed, for example, through reaction at a temperature of -20 to 70℃, in an organic solvent (e.g., dichloromethane, chloroform, 1,2-dichloro-ethane, toluene, diethyl ether and a mixture thereof), in the presence of hydrogen fluoride salts (e.g. triethylamine tris(hydrogen fluoride), pyridine hydrogen fluoride, potassium hydrogen bifluoride and the like).

[0144] In Reaction Scheme 4, Reaction 4-4 is an alkylation reaction of hydroxyl group which is known and is performed as described in Reaction Scheme 2, Reaction 2-1.

[0145] In Reaction Scheme 4, Reaction 4-5 is a deprotection reaction of protecting group which is known and is performed as described above.

[0146] In one aspect, a compound corresponding to the compound represented by formula (5d) can be produced by Reaction Scheme 5.

Reaction Scheme 5



[0147] Wherein PG represents a protecting group, and other symbols represent the same meaning as described above.

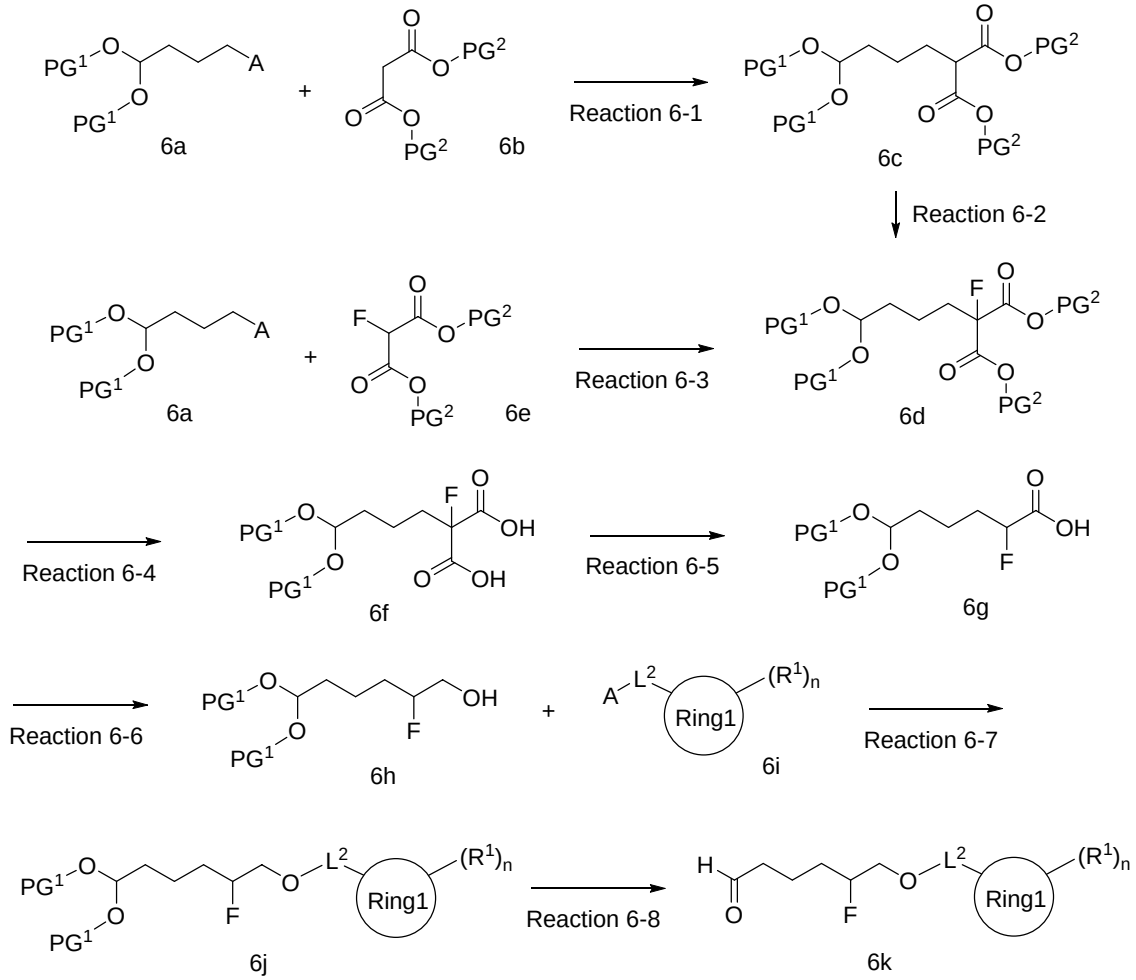
[0148] In Reaction Scheme 5, Reaction 5-1 is an ether formation reaction. The ether formation reaction is known, and is performed, for example, through reaction at a temperature of 20 to 100℃, in an organic solvent (e.g., t-BuOH, H_2O and a mixture thereof), in the presence of inorganic base (e.g. sodium hydroxide and the like) in the presence of a phase transfer catalyst (tetrabutylammonium iodide and the like).

[0149] In Reaction Scheme 5, Reaction 5-2 is a fluorination reaction. The fluorination reaction is known, and is performed, for example, through reaction at a temperature of -20 to 40℃, in an organic solvent (e.g., dichloromethane, THF, toluene and a mixture thereof), in the presence of fluorination agent (e.g. diethylamino-sulfur trifluoride, perfluorobutanesulfonyl fluoride, 2-pyridinesulfonyl fluoride and the like), in the presence or absence of a base (triethylamine, diisopropylethylamine, sodium carbonate, sodium bicarbonate, potassium carbonate and the like), in the presence or absence of hydrogen fluoride salts (e.g. triethylamine tris(hydrogen fluoride)).

[0150] In Reaction Scheme 5, Reaction 5-3 is a deprotection reaction of protecting group which is known and is performed as described above.

[0151] In one aspect, a compound corresponding to the compound represented by formula (6k) can be produced by Reaction Scheme 6.

Reaction Scheme 6



[0152] Wherein PG^1 represents a protecting group of aldehyde, PG^2 represents a protecting group of carboxylic acid, and other symbols represent the same meaning as described above.

[0153] In Reaction Scheme 6, Reaction 6-1 is an alkylation reaction of malonic acid diester. The alkylation reaction of malonic acid diester is known, and is performed, for example, through reaction at a temperature of 0 to 100℃, in an organic solvent (DMF, dimethyl sulfoxide, chloroform, dichloromethane, diethyl ether, THF, methyl t-butyl ether, and the like), in the presence of a base (e.g., sodium hydride, potassium t-butoxide, potassium carbonate and the like).

[0154] In Reaction Scheme 6, Reaction 6-2 is a fluorination reaction. The fluorination reaction is known, and is performed, for example, through reaction at a temperature of 0 to 100℃, in an organic solvent (diethyl ether, THF, methyl t-butyl ether, acetonitrile, DMF and the like), in the presence of fluorination agent (e.g. 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate), N-fluoro-

bis[(trifluoromethyl)sulfonyl]imide, N-fluorodibenzenesulfonimide and the like), in the presence or absence of a base (sodium hydride, lithium diisopropyl amide, cesium carbonate and the like).

[0155] In Reaction Scheme 6, Reaction 6-3 is an alkylation reaction of 2-fluoro malonic acid diester which is known and is performed as described in Reaction 6-1.

[0156] In Reaction Scheme 6, Reaction 6-4 is a deprotection reaction of protecting group which is known and is performed as described above.

[0157] In Reaction Scheme 6, Reaction 6-5 is a decarboxylation reaction. The thermal decarboxylation reaction is known, and is performed, for example, through reaction at a temperature of 20 to 200°C, in an organic solvent (DMF, dimethyl sulfoxide, pyridine and the like), in the presence or absence of a base (for example, triethylamine, diisopropylethylamine, lithium hydroxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, cesium carbonate, tripotassium phosphate, cesium fluoride, barium hydroxide, tetrabutylammonium fluoride), in the presence or absence of an organic acid (for example, acetic acid, trifluoroacetic acid, methanesulfonic acid, and p-tosylic acid) or an inorganic acid (for example, hydrochloric acid and sulfuric acid), or a mixture thereof.

[0158] In Reaction Scheme 6, Reaction 6-6 is a reduction of carboxylic acid. The reduction of carboxylic acid is known, and is performed, for example, through reaction at a temperature of 20 to 200°C, in an organic solvent (diethyl ether, THF, methyl t-butyl ether, and the like), in the presence of reducing agent (e.g. BH_3-SMe_2, BH_3-THF, $LiAlH_4$, and the like).

[0159] In Reaction Scheme 6, Reaction 6-7 is an alkylation reaction of hydroxyl group which is known and is performed as described in Reaction Scheme 2, Reaction 2-1.

[0160] In Reaction Scheme 6, Reaction 6-8 is a deprotection reaction of protecting group which is known and is performed as described above (for example, a deprotection reaction under an acidic condition).

[0161] In each reaction in the present specification, the compounds represented by formula 1a, 2a, 2b, 2d, 2e, 3a, 4a, 4c, 4e, 5a, 6a, 6b, 6e, and formula 6i, used as starting materials are known, or can be easily produced by combining known methods, for example, the methods described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 3rd Edition (Richard C. Larock, John Wiley & Sons Inc, 2018) and the like, or methods obtained by partially modifying known methods or the like.

[0162] Among the compounds of the present disclosure, a compound having optical activity can be produced by using a starting material or reagent having optical activity, or by optically

separating a racemic intermediate and then converting to the present disclosure compound therefrom, or optically separating a racemic form of the compound of the present disclosure.

[0163] This optical separation is known, and examples thereof include a method in which a salt, a complex, or the like is formed with another optically active compound, and then a target compound is isolated after recrystallization or directly separated using a chiral column or the like.

[0164] In the reactions in the present specification, a reaction involving heating can be performed using a water bath, an oil bath, a sand bath, or a microwave, as would be apparent to those skilled in the art.

[0165] In the reactions in the present specification, a solid-phase supported reagent that is supported on a polymer (for example, polystyrene, polyacrylamide, polypropylene, polyethylene glycol, and the like) may be appropriately used.

[0166] In the reactions in the present specification, the reaction product can be purified by ordinary purification means, for example, distillation under normal pressure or reduced pressure, high-performance liquid chromatography using silica gel or magnesium silicate, thin-layer chromatography, methods using an ion-exchange resin or a scavenger resin, column chromatography, washing, and recrystallization. The purification may be performed for each reaction or may be performed after completion of some reactions.

[Toxicity]

[0167] The toxicity of the compound of the present disclosure is low, and therefore can be used as a medicament safely.

[Application to medicament]

[0168] The compound of the present disclosure has GBA1 and GCS dual modulatory activity, and thus the compound of the present disclosure is useful as an agent for preventing and/or treating diseases associated with GBA1 and/or GCS, for example, Parkinson's disease, Lewy body disease, Gaucher disease, multiple system atrophy, Fabry disease, Niemann-Pick disease type C, lysosomal storage diseases, dementia, epilepsy, bipolar disorder, schizophrenia, anxiety disorder, major depression disorder, Sandhoff's disease, Tay-Sachs disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, cognitive impairment, learning disabilities, gait disorders, sleeping disorder, neurological disorders, CNS disorders, polycystic kidney disease,

type 2 diabetes, cancer, open angle glaucoma, endometriosis, multiple myeloma, virus infection, inflammation, systemic lupus erythematosus, hepatitis, Guillain-Barre Syndrome, diabetic nephropathy, skin disorder.

[0169] The disease associated with GBA1 and/or GCS is preferably Parkinson's disease, Lewy body disease, or Gaucher disease.

[0170] In the use of the compound of the present disclosure for the purpose of preventing and/or treating the above-mentioned diseases, the substance that acts as an active ingredient, is usually formulated together with a pharmaceutically acceptable carrier such as various additives or solvents, and then administered systemically or topically, orally or parenterally. Here, the pharmaceutically acceptable carrier means a substance other than the active ingredient, which is generally used for pharmaceutical preparation. The pharmaceutically acceptable carrier preferably does not exhibit a pharmacological action at the dosage of the preparation, is harmless, and does not interfere with the therapeutic effect of the active ingredient. The pharmaceutically acceptable carrier can also be used for the purpose of, for example, enhancing the usefulness of the active ingredient and the preparation, facilitating the formulation, stabilizing the quality, or improving the usability. Specifically, substances described in "Japanese Pharmaceutical Excipients Directory" published in 2021 by Yakuji Nippo Limited (edited by International Pharmaceutical Excipients Council Japan) and the like may be appropriately selected according to the purpose.

[0171] The compound of the present disclosure can be administered to a mammal (preferably human, more preferably a human patient) in a pharmaceutically effective amount.

[0172] Since the dosage of the compound of the present disclosure depends on age, body weight, symptom, desired therapeutic effect, route of administration, period of treatment, and the like, the dosage inevitably varies. The compound of the present disclosure is generally administered orally in the range of 0.1 ng to 1,000 mg per patient per administration, or parenterally administered or continuously administered intravenously in the range of 0.01 ng to 100 mg per patient per administration.

[0173] Needless to say, the dosage varies depending on various conditions as described above. Therefore, a dosage smaller than the above dosage may be sufficient, or a dosage beyond the above range may be required.

[0174] Examples of the dosage form thereof include preparations for oral administration (for example, tablets, capsules, granules, powders, oral solutions, syrups, and oral jellies), preparations for oral cavity (for example, oral tablets, oral sprays, oral semisolids, and oral

rinses), preparations for injection (for example, injectables), preparations for dialysis (for example, dialysis agents), preparations for inhalation (for example, inhalants), preparations for ophthalmic application (for example, eye drops and ophthalmic ointments), preparations for otologic application (for example, ear drops), preparations for nasal application (for example, nose drops), preparations for rectum (for example, suppositories, semisolids for rectum, and enemas for rectal application), preparations for vagina (for example, vaginal tablets and vaginal suppositories), and preparations for skin (for example, external solid agents, external liquid agents, sprays, ointments, creams, gels, and patches).

[Preparation for oral administration]

[0175] Examples of the preparation for oral administration include tablets, capsules, granules, powders, oral solutions, syrups, and oral jellies. The preparation for oral administration includes rapidly disintegrating preparations in which the releasability of the active ingredient from the preparation is not particularly adjusted; and controlled-release preparations such as enteric-coated preparations and sustained-release preparations in which the releasability is adjusted according to the purpose by unique formulation design and formulation method. The enteric-coated preparation refers to a preparation designed to release the active ingredient mainly in the small intestine without releasing the active ingredient in the stomach, for the purpose of preventing the degradation of the active ingredient in the stomach or reducing the irritation of the active ingredient to the stomach. The enteric-coated preparation can be usually produced by coating with an acid-insoluble enteric-coated base. The sustained-release preparation refers to a preparation in which the release rate, release time, and release site of the active ingredient from the preparation are adjusted for the purpose of reducing the number of administrations or attenuating side effects. The sustained-release preparation can be usually produced by using an appropriate sustained-release agent. Among preparations for oral administration, capsules, granules, tablets, and the like can be coated with an appropriate coating agent such as a saccharide, a sugar alcohol, or a polymer compound, for the purpose of, for example, facilitating ingestion or preventing degradation of the active ingredient.

(1) Tablet

[0176] The tablet is a solid preparation that is administered orally and has a certain shape. The tablet includes those generally referred to as tablets, such as uncoated tablets, film-coated

tablets, sugar-coated tablets, multilayer tablets, and dry-coated tablets, as well as orally rapidly disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets, and soluble tablets. In the production of the uncoated tablet, the following method (a), (b), or (c) is usually used:

(a) Additives such as an excipient, a binder, and a disintegrant are added to the active ingredient and mixed to prepare a homogeneous mixture, the mixture is granulated by an appropriate method using water or a solution containing a binder, then a lubricant or the like is added to the granulated product and mixed, and the resulting mixture was compression-molded;

(b) Additives such as an excipient, a binder, and a disintegrant are added to the active ingredient and mixed to prepare a homogeneous mixture, and the mixture is directly compression-molded; or the active ingredient, a lubricant, and the like are added to granules prepared in advance with additives to prepare a homogeneous mixture, and then the mixture is compression-molded; and

(c) Additives such as an excipient and a binder are added to the active ingredient and mixed to prepare a homogeneous mixture, a kneaded product obtained by wetting the mixture with a solvent is poured into a predetermined mold and molded, and then the molded product is dried by an appropriate method.

[0177] The film-coated tablet can be usually produced by thinly coating an uncoated tablet with an appropriate coating agent such as a polymer compound. The sugar-coated tablet can be usually produced by coating an uncoated tablet with a coating agent containing a saccharide or a sugar alcohol. The multilayer tablet can be produced by forming layers of powder particles having different compositions and compression-molding the layered powder particles by an appropriate method. The dry-coated tablet can be produced by covering an inner core tablet with an outer layer having a composition different from that of the inner core tablet. The tablet can also be an enteric-coated tablet or a sustained-release tablet by a known appropriate method. The orally rapidly disintegrating tablet, the chewable tablet, the effervescent tablet, the dispersible tablet, and the soluble tablet are those in which unique functions are imparted to the tablets by appropriate selection of additives, and can be produced according to the above-described methods for producing the tablet. Incidentally, the orally rapidly disintegrating tablet refers to a tablet that can be taken by being rapidly dissolved or disintegrated in the oral cavity; the chewable tablet refers to a tablet that is chewed and taken; the effervescent tablet refers to a tablet that dissolves or disperses while

rapidly foaming in water; the dispersible tablet refers to a tablet that is taken by being dispersed in water; and the soluble tablet refers to a tablet that is taken by being dissolved in water. The effervescent tablet can be produced by using an appropriate acidic substance, a carbonate, a bicarbonate, or the like as an additive.

(2) Capsule

[0178] The capsule is a preparation in which ingredients are filled in a capsule or encapsulated with a capsule base, and includes hard capsules, soft capsules, and the like. The hard capsule can be produced by adding an additive such as an excipient to the active ingredient and mixing them to prepare a homogeneous mixture, or forming the mixture into particles or a molded product by an appropriate method, and filling, in a capsule, the mixture, the particles, or the molded product as it is or after each content is slightly molded. The soft capsule can be produced by encapsulating a mixture of the active ingredient and an additive in a certain shape with an appropriate capsule base such as gelatin having increased plasticity by adding glycerin, D-sorbitol, or the like. The capsule may be an enteric-coated capsule or a sustained-release capsule prepared by a known appropriate method, and a colorant, a preservative, or the like may be added to the capsule base.

(3) Granule

[0179] The granule is a preparation granulated in a granular form, and includes effervescent granules and the like in addition to those generally referred to as granules. In the production of the granule, the following method (a), (b), or (c) is usually used:

(a) An excipient, a binder, a disintegrant, or other additives are added to a powdery active ingredient and mixed to prepare a homogeneous mixture, and then the mixture is granulated by an appropriate method;

(b) An additive such as an excipient is added to the active ingredient prepared in a granular form in advance, and mixed to prepare a homogeneous mixture; and

(c) An additive such as an excipient is added to the active ingredient prepared in a granular form in advance and mixed, and the mixture is then formed into granules by an appropriate method.

[0180] The granule may be coated as necessary, and may be an enteric-coated granule or a sustained-release granule prepared by a known appropriate method. The effervescent granule can be produced by using an appropriate acidic substance, a carbonate, a bicarbonate,

or the like as an additive. The effervescent granule refers to a granule that dissolves or disperses while rapidly foaming in water. The granule can also be made into a fine granule by adjusting the size of the particle.

(4) Powder

[0181] The powder is a powdery preparation, and can be usually produced by adding an excipient or other additives to the active ingredient and mixing them to prepare a homogeneous mixture.

(5) Oral solution

[0182] The oral solution is a liquid or flowable viscous gel preparation, and includes, in addition to those generally referred to as oral solutions, an elixir, a suspension, an emulsion, a lemonade, and the like. The oral solution can be usually produced by adding an additive and purified water to the active ingredient, followed by mixing, uniformly dissolving or emulsifying or suspending, and filtering as necessary. The elixir refers to a clear liquid oral solution containing sweet and aromatic ethanol. The elixir can be usually produced by adding ethanol, purified water, a flavoring agent, and white sugar, other saccharides or a sweetener to a solid active ingredient or a leachate thereof, dissolving components, and preparing a clear liquid by filtration or other methods. The suspension refers to an oral solution in which the active ingredient is finely and homogeneously suspended. The suspension can be usually produced by adding a suspending agent or other additives and purified water or oil to a solid active ingredient, and performing suspension by an appropriate method to homogenize the entire active ingredient. The emulsion refers to an oral solution in which the active ingredient is finely and homogeneously emulsified. The emulsion can be usually produced by adding an emulsifier and purified water to a liquid active ingredient, and performing emulsification by an appropriate method to homogenize the mixture. The lemonade refers to a clear liquid oral solution having a sweet taste and a sour taste.

(6) Syrup

[0183] The syrup is a viscous liquid preparation or solid preparation containing a saccharide or sweetener, and includes preparations for syrup and the like. The syrup can be usually produced by adding the active ingredient to a solution of white sugar, other saccharides or a sweetener, or a single syrup, followed by dissolving, mixing, suspending, or emulsifying, and

if necessary, boiling the mixed liquid, followed by hot filtration. The preparation for syrup refers to a granular or powdery preparation that becomes a syrup when water is added, and may also be referred to as a dry syrup. The preparation for syrup can be usually produced using a saccharide or a sweetener as an additive in accordance with the method for producing the granule or powder.

(7) Oral jelly

[0184] The oral jelly is a formed gel preparation having no fluidity, and can be usually produced by adding an additive and a polymer gel base to the active ingredient and mixing them, gelatinizing the mixture by an appropriate method, and forming the resulting gel into a certain shape.

[Preparation for injection]

(1) Injectable

[0185] The injectable is a solution, a suspension or an emulsion, or a solid sterile preparation to be dissolved or suspended when used, which is administered subcutaneously, intramuscularly, or directly administered to a body tissue such as blood vessel or an organ. The injectable includes a lyophilized injectable, a powder injectable, a filled syringe, a cartridge, an infusion, an embedded injectable, a long acting injectable, and the like, in addition to those generally referred to as injectables. In the production of the injectable, the following method (a), (b), or (c) is usually used:

(a) A homogeneous solution is prepared by dissolving, suspending, or emulsifying the active ingredient as it is or a mixture obtained by adding an additive to the active ingredient, in water for injection, another aqueous solvent, a non-aqueous solvent or the like. Then, the prepared solution is filled in a container for injection, and then the container is sealed, followed by sterilization; and

(b) A homogeneous solution is prepared by dissolving, suspending, or emulsifying the active ingredient as it is or a mixture obtained by adding an additive to the active ingredient, in water for injection, another aqueous solvent, a non-aqueous solvent or the like. Then, the prepared solution is aseptically filtrated or aseptically prepared, the resulting solution is filled in a container for injection, and the container is sealed.

[0186] The lyophilized injectable can be usually produced by dissolving the active ingredient as it is or a mixture of the active ingredient and an additive such as an excipient, in

water for injection, aseptically filtering the solution, filling the solution in a container for injection, and then lyophilizing the solution, or directly filling the solution in a container after lyophilizing the solution in a dedicated container. The powder injectable can be usually produced by crystallizing a powder subjected to aseptic filtration to prepare a powder, and if necessary, adding a sterilized additive to the prepared powder, and filling the powder in a container for injection. A filled syringe can be usually produced by preparing a solution, a suspension, or an emulsion with the active ingredient as it is or with the active ingredient and an additive, and then filling the prepared solution, suspension, or emulsion in a glass syringe. The cartridge refers to an injectable used by inserting a cartridge filled with a drug solution into a dedicated syringe. The cartridge filled with the drug solution can be usually produced by preparing a solution, a suspension, or an emulsion with the active ingredient as it is or with the active ingredient and an additive, and filling the prepared solution, suspension, or emulsion into the cartridge. The infusion refers to 100 mL or more of injectable usually administered intravenously. The embedded injectable refers to a solid or gel-like injection which is applied subcutaneously, intramuscularly or the like by using an implantation tool or by surgery, for the purpose of releasing the active ingredient over a long period of time. The embedded injectable can be usually produced by using a biodegradable polymer compound and forming the compound into a pellet, microsphere, or gel. The long acting injectable refers to an injectable which is applied intramuscularly or the like for the purpose of releasing the active ingredient over a long period of time. The sustained injectable can be usually produced by dissolving or suspending the active ingredient in a vegetable oil or the like, or preparing a microsphere suspension containing a biodegradable polymer compound.

[0187] The compound of the present disclosure may also be administered as a concomitant drug in combination with another drug for:

1) complementation and/or enhancement of the prophylactic and/or therapeutic effects of the compound;

2) improvement of kinetics and absorption, and reduction in dosage; and/or

3) attenuation of side effects of the compound.

[0188] With respect to a combination drug comprising the compound of the present invention and other drug, may be administered in the form of a blending drug in which both ingredients are blended in one preparation, or may be administered in the form of separate preparations. Administration in these separate preparations includes simultaneous administration and administration by time difference. In addition, administration by time

difference may be performed by administering the compound of the present disclosure first and then administering another drug later, or by administering another drug first and then administering the compound of the present disclosure later. The administration methods of the drugs may be the same or different.

[0189] The disease for which the above combination drug has a prophylactic and/or therapeutic effect is not particularly limited as long as it is a disease for which the prophylactic and/or therapeutic effect of the compound of the present disclosure are complemented and/or enhanced.

[0190] Other drugs for complementing and/or enhancing the prophylactic and/or therapeutic effect of the compound of the present disclosure on Parkinson's disease include, for example, levodopa, carbidopa, pramipexole, ropinirole, rotigotine, apomorphine, zonisamide, droxidopa, cabergoline, pergolide, tolcapone, entacapone, selegiline, rasagiline, safinamide, istradefylline, foslevodopa/foscarbidopa, benserazide, bromocriptine, talipexole, amantadine, trihexyphenidyl, and biperiden.

[0191] Other drugs for complementing and/or enhancing the prophylactic and/or therapeutic effect of the compound of the present disclosure on Lewy body disease include, for example, donepezil hydrochloride, rivastigmine, and zonisamide.

[0192] Other drugs for complementing and/or enhancing the prophylactic and/or therapeutic effect of the compound of the present disclosure on Gaucher disease include, for example, imiglucerase, velaglucerase alfa, eliglustat, alglucerase, and miglustat.

[0193] Any two or more of the other drugs may be administered in combination.

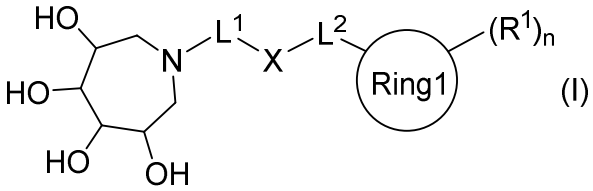
[0194] In addition, other drugs that complement and/or enhance the prophylactic and/or therapeutic effect of the compound of the present disclosure include not only those that have been found to date but also those that will be found in the future based on the mechanism described above.

[0195] Unless defined otherwise, all technical, scientific terms, and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0196] In addition, in the present specification, all contents of all patent documents and non-patent documents or references explicitly cited may be cited herein as part of the present specification.

[0197] In one aspect, the present disclosure provides the following embodiments.

[0198] [1] A compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[0199] wherein

[0200] L^1 represents (1) a C4-7 alkylene, (2) a C4-7 alkenylene, or (3) a C4-7 alkynylene,

[0201] L^1 may be substituted with one to five R^{L1}s,

[0202] R^{L1} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, or (10) a hydroxyl group,

[0203] a plurality of R^{L1}s may be the same or different,

[0204] L^2 represents (1) a C1-3 alkylene, (2) a C2-3 alkenylene or (3) a C2-3 alkynylene,

[0205] L^2 may be substituted with one to four R^{L2}s,

[0206] R^{L2} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, or (10) a hydroxyl group,

[0207] a plurality of R^{L2}s may be the same or different,

[0208] X represents (1) a bond, (2) -O-, (3) -S-, (4) -SO-, or (5) $-SO_2-$,

[0209] Ring 1 represents (1) a benzene ring (2) a naphthalene ring or (3) a 5- to 10-membered heterocyclyl,

[0210] R^1 represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, (10) a C5-7 carbocyclyl, (11) a 5- to 7-membered heterocyclyl, (12) -O-(C5-7 carbocyclyl), or (13) -O-(5- to 7-membered heterocyclyl),

[0211] a plurality of R^1s may be the same or different,

[0212] the groups (2) to (13) in R^1 may be substituted with one to five R^{1-1}s,

[0213] R^{1-1} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6

haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, (10) a C1-6 alkyl sulfonyl group, (11) a cyano group, or (12) a phenyl group,

[0214] a plurality of R^{1-1}s may be the same or different,

[0215] the symbol:



[0216] represents that a substituent is bonded to the α-configuration, β-configuration or a mixture of α- and β-configurations at an appropriate ratio, and

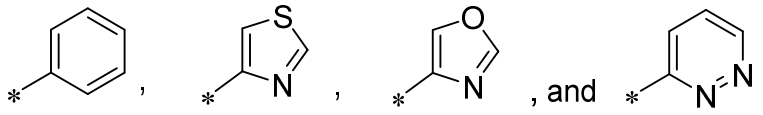
[0217] n represents an integer of 0 to 5.

[0218] [2] The compound according to the above [1] or a pharmaceutically acceptable salt thereof, wherein L^1 represents a hexylene group.

[0219] [3] The compound according to the above [1] or [2] or a pharmaceutically acceptable salt thereof, wherein X represents -O-.

[0220] [4] The compound according to any one of the above [1] to [3] or a pharmaceutically acceptable salt thereof, wherein L^2 represents a methylene group.

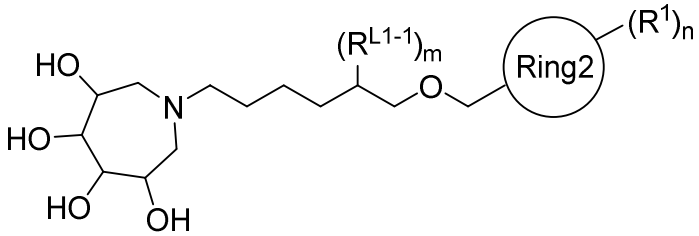
[0221] [5] The compound according to any one of the above [1] to [4] or a pharmaceutically acceptable salt thereof, wherein Ring 1 represents a ring structure selected from the group consisting of the following ring structures;



[0222] wherein the * mark represents a bonding position with L^2.

[0223] [6] The compound according to any one of the above [1] to [5] or a pharmaceutically acceptable salt thereof, wherein R^{L1} represents (1) a halogen atom, or (2) a C1-6 alkyl group.

[0224] [7] The compound according to any one of the above [1] to [6] or a pharmaceutically acceptable salt thereof, wherein the compound represented by formula (I) is a compound represented by formula (I-1):



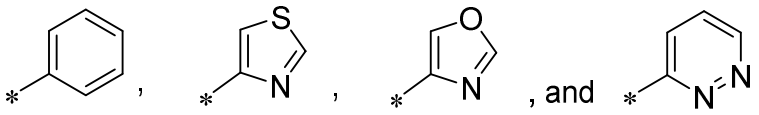
(I-1)

[0225] wherein R^{L1-1} represents (1) a halogen atom, or (2) a C1-6 alkyl group,

[0226] a plurality of R^{L1-1}s may be the same or different,

[0227] m represents an integer of 1 to 2,

[0228] Ring 2 represents a ring structure selected from the group consisting of the following ring structures;



[0229] wherein the * mark represents a bonding position with methylene, and

[0230] other symbols represent the same meaning as the symbols described in the above [1].

[0231] [8] The compound according to any one of the above [1] to [7] or a pharmaceutically acceptable salt thereof, wherein the compound represented by formula (I) is a compound selected from the group consisting of:

[0232] (1) (3S,4R,5R,6S)-1-{6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol,

[0233] (2) (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol,

[0234] (3) (3S,4R,5R,6S)-1-{(5R)-6-[(3-ethoxy-4-fluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

[0235] (4) (3S,4R,5R,6S)-1-{(5S)-6-[(3-ethoxy-4-fluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

[0236] (5) (3S,4R,5R,6S)-1-[(5R)-5-fluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol,

[0237] (6) (3S,4R,5R,6S)-1-[(5S)-5-fluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol,

[0238] (7) (3S,4R,5R,6S)-1-[(5R)-6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol,

[0239] (8) (3S,4R,5R,6S)-1-[(5S)-6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol,

[0240] (9) (3S,4R,5R,6S)-1-{(5S)-6-[(4-ethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

[0241] (10) (3S,4R,5R,6S)-1-{(5R)-6-[(4-ethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

[0242] (11) (3S,4R,5R,6S)-1-{(5S)-6-[(4-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

[0243] (12) (3S,4R,5R,6S)-1-{(5R)-6-[(4-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

[0244] (13) (3S,4R,5R,6S)-1-{(5S)-5-fluoro-6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol,

[0245] (14) (3S,4R,5R,6S)-1-{(5R)-5-fluoro-6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol,

[0246] (15) (3S,4R,5R,6S)-1-[(5S)-6-{[6-(3,5-difluorophenyl)-3-pyridazinyl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol, and

[0247] (16) (3S,4R,5R,6S)-1-[(5R)-6-{[6-(3,5-difluorophenyl)-3-pyridazinyl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol.

[0248] [9] A pharmaceutical composition comprising the compound according to any one of the above [1] to [8] or a pharmaceutically acceptable salt thereof as an active ingredient, and a pharmaceutically acceptable carrier.

[0249] [10] The pharmaceutical composition according to the above [9], which is a GBA1 chaperone modulator.

[0250] [11] The pharmaceutical composition according to the above [9], which is a GCS inhibitor.

[0251] [12] The pharmaceutical composition according to the above [9], which is a GBA1 and GCS dual modulator.

[0252] [13] The pharmaceutical composition according to any one of the above [9] to [12], which is an agent for treating and/or preventing a disease associated with GBA1 and/or GCS.

[0253] [14] The pharmaceutical composition according to the above [13], wherein the disease associated with GBA1 and/or GCS is selected from the group consisting of Parkinson's disease, Lewy body disease, Gaucher disease, Multiple system atrophy, Fabry disease, Niemann-Pick disease type C, lysosomal storage diseases, Dementia, epilepsy, bipolar disorder, schizophrenia, anxiety disorder, major depression disorder, Sandhoff's disease, Tay-Sachs disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, cognitive impairment, learning disabilities, gait disorders, sleeping disorder, neurological disorders, CNS disorders, polycystic kidney disease, type 2 diabetes, cancer, open angle glaucoma, endometriosis, multiple myeloma, virus infection, inflammation, systemic lupus erythematosus, hepatitis, Guillain-Barre Syndrome, diabetic nephropathy, and skin disorder.

[0254] [15] The pharmaceutical composition according to the above [13], wherein the disease associated with GBA1 and/or GCS is selected from the group consisting of Parkinson's disease, Lewy body disease, and Gaucher disease.

[0255] [16] The pharmaceutical composition according to the above [9], wherein the pharmaceutical composition is administered in combination with one or more agent(s) selected from the group consisting of levodopa, carbidopa, pramipexole, ropinirole, rotigotine, apomorphine, zonisamide, droxidopa, cabergoline, pergolide, tolcapone, entacapone, selegiline, rasagiline, safinamide, istradefylline, foslevodopa/foscarbidopa, benserazide, bromocriptine, talipexole, amantadine, trihexyphenidyl, biperiden, donepezil hydrochloride, imiglucerase, velaglucerase alfa, eliglustat, alglucerase, and miglustat.

[0256] [17] An agent for treating and/or preventing a disease associated with GBA1 and/or GCS, comprising the compound according to any one of the above [1] to [8] or a pharmaceutically acceptable salt thereof.

[0257] [18] A method for preventing and/or treating a disease associated with GBA1 and/or GCS, the method comprising administering the compound according to any one of the above [1] to [8] or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to the above [9] to a patient in need of prevention and/or treatment of a disease associated with GBA1 and/or GCS.

[0258] [19] A compound according to any one of the above [1] to [8] or a pharmaceutically acceptable salt thereof, for use in preventing and/or treating a disease associated with GBA1 and/or GCS.

[0259] [20] Use of the compound according to any one of the above [1] to [8] or a pharmaceutically acceptable salt thereof, for manufacturing an agent for preventing and/or treating a disease associated with GBA1 and/or GCS.

[Synthesis Examples]

[0260] The solvent in parentheses shown in the description of the separation by chromatography and TLC indicates an eluting solvent or developing solvent used therefor, and the ratio represents the volume ratio.

[0261] The solvent in parentheses shown in the description of NMR indicates the solvent used for the measurement.

[0262] The compound names used in the present specification are named using a computer program ACD/Name (registered trademark), which generally performs naming according to the IUPAC nomenclature, or using a Chemdraw Ultra (Version 12.0, manufactured by Cambridge Soft), or according to the IUPAC nomenclature.

[0263] LC-MS analysis was performed under the following conditions.

[0264] **Method A:** Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2020 with ESI source. MS parameters were as follows: Mobile Phase: 1.5ML/4LTFA in water (solvent A) and 0.75ML/4LTFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.5mL/min; Column: Agilent Pursit 5 C18 20*2.0mm; Wavelength: UV 220nm, 254nm; Column temperature: 50℃; MS ionization: ESI.

[0265] **Method B:** Rersed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.8mL/4L $NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B), sing the elution gradient 10%-80% (solvent B) over 2 minutes and holding at 80% for 0.48minutes at a flow rate of 1.2mL/min; Column: Xbridge C18 2.1*50mm 5μm; Wavelength: UV 220nm & 254nm; Column temperature: 50℃; MS ionization: ESI.

[0266] **Method C:** Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.8mL/4L $NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B), sing the elution gradient 10%-80% (solvent B) over 6 minutes and holding at 80% for 0.5minutes at a flow rate of 0.8mL/min; Column: Xbridge C18 2.1*50mm 5μm; Wavelength: UV 220nm & 254nm; Column temperature: 50℃; MS ionization: ESI.

[0267] Preparative HPLC was performed under the following conditions or with different solvent gradients and columns.

[0268] **Prep-HPLC (HCl)**:

[0269] Mobile Phase: 0.1% HCl in water (solvent A) and acetonitrile (solvent B), using the elution gradient 25%-55% (solvent B) over 8 minutes then holding at 100% for 2 minutes, at a flow rate of 30mL/min; Column: Phenomenex Synergi C18 150*30mm*4μm.

[0270] **Prep-HPLC (FA)**:

[0271] Mobile Phase: 0.225% FA in water (solvent A) and acetonitrile (solvent B), using the elution gradient 55%-85% (solvent B) over 8 minutes then holding at 100% for 2 minutes, at a flow rate of 30mL/min; Column: Welch Xtimate C18 100*40mm*3μm.

[0272] **Prep-HPLC (base):**

[0273] Mobile Phase: 0.05% NH_3H_2O and 10 mM NH_4HCO_3 in water (solvent A) and acetonitrile (solvent B), using the elution gradient 30%-60% (solvent B) over 20 minutes then holding at 100% for 5 minutes, at a flow rate of 30mL/min; Column: Xtimate C18 150*40mm*5μm.

[0274] **Prep-HPLC (neutral):**

[0275] Mobile Phase: 10 mM NH_4HCO_3 in water (solvent A) and acetonitrile (solvent B), using the elution gradient 35%-65% (solvent B) over 9.5 minutes then holding at 100% for 2 minutes, at a flow rate of 30ml/min; Column: Phenomenex Gemini C18 75*40 mm*3 μm.

[0276] SFC analysis was performed under the following conditions.

[0277] Preparative SFC was performed under conditions similar to analytical method or with different Mobile phase, gradients, and columns.

[0278] **Method A1:**

[0279] Waters UPCC with PDA Detector, Column: Cellulose 2 150*4.6mm I.D., 5μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA) Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0280] **Method A2:**

[0281] Waters UPCC with PDA Detector, Column: Cellulose 2 100*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Isocratic: 40% B, Flow rate: 2.8mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0282] **Method A3:**

[0283] Waters UPCC with PDA Detector, Column: Cellulose 2 150*4.6mm I.D., 5μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Isocratic: 40% B, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0284] **Method B1:**

[0285] Waters UPCC with PDA Detector, Column: Chiralpak AD-3 150*4.6mm I.D., 3μm, Mobile phase: 50% of ethanol (0.05% DEA) in CO_2, Flow rate: 2.2mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0286] **Method B2:**

[0287] Waters UPCC with PDA Detector, Column: Chiralpak AD-3 150*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 4 min and hold 40% for 2 min, then 5% of B for 2 min, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0288] **Method B3:**

[0289] Waters UPCC with PDA Detector, Column: Chiralpak AD-3 150*4.6mm I.D., 3μm, Mobile phase: 40% of methanol (0.05% DEA) in CO_2, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0290] **Method B4:**

[0291] Agilent 1260 with DAD detector, Column: Chiralpak AD-3 150*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Gradient: from 5% to 40% of B in 5.5 min and hold 40% for 3 min, then 5% of B for 1.5 min, Flow rate: 2.5mL/min, Column temp.: 40℃, ABPR: 1500psi.

[0292] **Method B5:**

[0293] Waters UPCC with PDA Detector, Column: Chiralpak AD-3 150*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Gradient: from 5% to 40% of B in 5 min and hold 40% for 2.5 min, then 5% of B for 2.5 min, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0294] **Method B6:**

[0295] Agilent 1260 with DAD detector, Column: Chiralpak AD-3 150*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Isocratic: 40% B, Flow rate: 2.5mL/min, Column temp.: 40℃, ABPR: 1500psi.

[0296] **Method B7:**

[0297] Agilent 1260 with DAD detector, Column: Chiralpak AD-3 50*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Isocratic: 40% B, Flow rate: 4mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0298] **Method B8:**

[0299] Waters UPCC with PDA Detector, Column: Chiralpak AS-3 150*4.6mm I.D., 3μm, Mobile phase: 40% of iso-propanol (0.05% DEA) in CO_2, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0300] **Method D1:**

[0301] Waters UPCC with PDA Detector, Column: Chiralcel OD-3 150*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 4 min and hold 40% for 2 min, then 5% of B for 2 min, Flow rate: 2.5mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0302] **Method E1:**

[0303] Waters UPCC with PDA Detector, Column: Chiralcel OJ-3 100*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 4 min and hold 40% for 0.5 min, then 5% of B for 1.5 min, Flow rate: 2.8mL/min, Column temp.: 35℃, ABPR: 1500psi.

[0304] **Method F1:**

[0305] Waters UPCC with PDA Detector, Column: Chiralpak IG-3 100*4.6mm I.D., 3μm, Mobile phase: 40% of ethanol (0.05% DEA) in CO_2, Flow rate: 2.8mL/min, Column temp.: 35°C, ABPR: 1500psi.

[0306] **Method F2:**

[0307] Waters UPCC with PDA Detector, Column: Chiralpak IG-3 50*4.6mm I.D., 3μm, Mobile phase: 40% of ethanol (0.05% DEA) in CO_2, Flow rate: 4mL/min, Column temp.: 35°C, ABPR: 1500psi.

[0308] **Method F3:**

[0309] Agilent 1260 with DAD detector, Column: Chiralpak IG-3 100*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 4 min and hold 40% for 2.5 min, then 5% of B for 1.5 min, Flow rate: 2.8mL/min, Column temp.: 35°C, ABPR: 1500psi.

[0310] **Method F4:**

[0311] Waters UPCC with PDA Detector, Column: Chiralpak IG-3 50*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Gradient: from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min, Flow rate: 4mL/min, Column temp.: 35°C, ABPR: 1500psi.

[0312] **Method F5:**

[0313] Agilent 1260 with DAD detector, Column: Chiralpak IG-3 100*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: methanol (0.05% DEA), Gradient: from 5% to 40% of B in 4 min and hold 40% for 3 min, then 5% of B for 1 min, Flow rate: 2.5mL/min, Column temp.: 40°C, ABPR: 1500psi.

[0314] **Method F6:**

[0315] Waters UPCC with PDA Detector Column: Chiralpak IG-3 50*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: iso-propanol (0.05% DEA), Isocratic: 40% B, Flow rate: 4mL/min, Column temp.: 35°C, ABPR: 1500psi.

[0316] **Method G1:**

[0317] Agilent 1260 with DAD detector, Column: Cellulose-4 100*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 4min and hold 40%, for 2.5 min, then 5% of B for 1.5min, Flow rate: 2.8mL/min Column temp.: 40°C, Back pressure: 100 bar.

[0318] **Method G2:**

[0319] Agilent 1260 with DAD detector, Column: Cellulose-4 100*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Isocratic: 40% B, Flow rate: 2.8mL/min Column temp.: 40℃, Back pressure: 100 bar.

[0320] **Method H1:**

[0321] Agilent 1260 with DAD detector, Column: ChiralPak AY-3 150*4.6mm I.D., 3μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 5.5min and hold 40%, for 3 min, then 5% of B for 1.5 min, Flow rate: 2.5mL/min, Column temp.: 40℃, ABPR: 100 bar.

[0322] **Method J1:**

[0323] Agilent 1260 with DAD detector, Column: Chiralcel OJ-H 150*4.6mm I.D., 5μm, Mobile phase: A: CO_2 B: ethanol (0.05% DEA), Gradient: from 5% to 40% of B in 4.5 min then 5% of B for 1.5 min, Flow rate: 2.5mL/min, Column temp.: 40℃, ABPR: 1500psi.

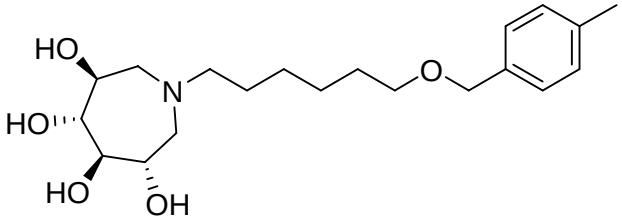
[0324] Abbreviations which have been used in the descriptions of following examples are: FA is formic acid; TFA is trifluoromethyl acetic acid; TEA is triethylamine; DIEA is N,N-diisopropylethylamine; DIAD is diisopropyl diazene-1,2-dicarboxylate; DAST is diethylaminosulfur trifluoride; DCM is dichloromethane; DMF is N,N-dimethylformamide; DMSO is dimethyl sulfoxide; EtOAc is ethyl acetate; PE is Petroleum Ether; THF is tetrahydrofuran; DMP is Dess-Martin Periodinane; $Pd(dppf)Cl_2$ is [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); TBAI is tetrabutylammonium iodide; TBAF is tetrabutylammonium fluoride; DMAP is N,N-dimethyl-4-aminopyridine; IPA is isopropanol; MTBE is methyl tert-butyl ether; NFSI is N-fluorobis(phenylsulfonyl)amine; PBSF is perfluoro-1-butanesulfonyl fluoride; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; DMA is N,N-Dimethylacetamide; TBAB is tetrabutylammonium bromide; mCPBA is m-chloroperoxybenzoic acid.

[0325] Reference Example 1: 6-iodohexyl 4-methylbenzyl ether

[0326] To a mixture of (4-methylphenyl)methanol (CAS No. 589-18-4, 0.16ml) and *t*-BuOK (207mg) in THF (5ml) was added 1,6-diiodohexane (CAS No. 629-09-4, 0.61mL) at 25℃. The reaction mixture was stirred at 40℃ for 14h. The mixture was diluted with DCM and concentrated to dryness. The crude product was purified by flash column with silica gel (PE to 15% EtOAC in PE) to give the title compound (103mg).

[0327] ^1H NMR ($CDCl_3$) δ: 7.29, 7.24, 4.48, 3.54-3.44, 3.19, 2.49-2.33, 1.94-1.82, 1.66-1.57, 1.53-1.37.

[0328] Example 1: (3S,4R,5R,6S)-1-{6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol



[0329] To a mixture of KI (57mg) in DMF (2mL) was added the compound prepared in Reference Example 1 (103mg), (3S,4R,5R,6S)-azepane-3,4,5,6-tetrol hydrochloride salt (CAS No. 170210-58-9, 93mg) and DIEA (0.26mL) at 25℃. The reaction was stirred at 80℃ for 16h. The residue was purified by prep-HPLC (base) to give the title compound (67mg).

[0330] LCMS: retention time 1.622 min, (Method B); MS (ESI, Pos.): m/z 368.2 (M+H)+; ^{1}H NMR ($CDCl_3$) δ: 7.26, 7.18, 4.45, 3.72-3.65, 3.60-3.53, 3.44, 2.89, 2.60, 2.53, 2.34, 1.63-1.55, 1.52-1.43, 1.41-1.34, 1.33-1.26.

[0331] Example 2 to 60

[0332] Example 2 to 60 were synthesized according to procedures analogous to Reference Example 1 and Example 1 using the corresponding alcohol compound instead of (4-methylphenyl)methanol.

[0333] Example 2: (3S,4R,5R,6S)-1-[6-(4-biphenylylmethoxy)hexyl]-3,4,5,6-azepanetetrol

[0334] LCMS: retention time 1.835 min, (Method B); MS (ESI, Pos.): m/z 430.3 (M+H)+;

[0335] ^{1}H NMR (CD_3OD) δ: 7.62-7.54, 7.48-7.36, 7.37-7.30, 4.54, 3.60-3.50, 3.42-3.36, 2.80, 2.56-2.49, 1.69-1.60, 1.50-1.31.

[0336] Example 3: (3S,4R,5R,6S)-1-{6-[(3-phenyl-2-propyn-1-yl)oxy]hexyl}-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0337] LCMS: retention time 0.67 min, (Method A); MS (ESI, Pos.): m/z 378.1 (M+H)+;

[0338] ^{1}H NMR (D_2O) δ: 7.44, 7.39-7.29, 4.33, 4.10-3.95, 3.76-3.44, 3.39-3.07, 1.72-1.52, 1.38-1.27.

[0339] Example 4: (3S,4R,5R,6S)-1-(6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0340] LCMS: retention time 0.692 min, (Method A); MS (ESI, Pos.): m/z 455.2 (M+H)+;

[0341] ^{1}H NMR ($CDCl_3$) δ: 7.95-7.89, 7.20, 7.20-7.08, 4.65, 4.48-3.75, 3.66, 3.66-3.51, 2.84-2.81, 2.59-2.46, 1.66-1.60, 1.46-1.26.

[0342] Example 5: (3S,4R,5R,6S)-1-{6-[(2-phenyl-1,3-thiazol-4-yl)methoxy]hexyl}-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0343] LCMS: retention time 0.688 min, (Method A); MS (ESI, Pos.): m/z 437.1 (M+H)+;

[0344] ^{1}H NMR (CD_3OD) δ: 8.05-7.95, 7.54-7.52, 4.68, 4.21-4.04, 3.86, 3.69-3.55, 3.44-3.36, 3.29-3.14, 1.90-1.65, 1.56-1.40.

[0345] Example 6: (3S,4R,5R,6S)-1-[6-({2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}methoxy)hexyl]-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0346] LCMS: retention time 0.751 min, (Method A); MS (ESI, Pos.): m/z 505.1 (M+H)+;

[0347] ^{1}H NMR (CD_3OD) δ: 8.17, 7.82, 7.59, 4.71, 4.22-4.08, 3.88, 3.70-3.59, 3.48-3.38, 3.31-3.16, 1.91-1.67, 1.59-1.43.

[0348] Example 7: (3S,4R,5R,6S)-1-[6-({2-[3-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}methoxy)hexyl]-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0349] LCMS: retention time 0.75 min, (Method A); MS (ESI, Pos.): m/z 505.1 (M+H)+;

[0350] ^{1}H NMR (CD_3OD) δ: 8.29, 8.21, 7.83, 7.74, 7.58, 4.71, 4.21-4.05, 3.90-3.85, 3.68-3.55, 3.46-3.35, 3.29-3.14, 1.87-1.65, 1.58-1.38.

[0351] Example 8: (3S,4R,5R,6S)-1-(6-{[2-(3-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0352] LCMS: retention time 0.698 min, (Method A); MS (ESI, Pos.): m/z 455.1 (M+H)+;

[0353] ^{1}H NMR (CD_3OD) δ: 7.86-7.71, 7.61-7.48, 7.30-7.20, 4.68, 4.19-4.02, 3.84, 3.65-3.57, 3.45-3.34, 3.27-3.14, 1.92-1.63, 1.57-1.37.

[0354] Example 9: (3S,4R,5R,6S)-1-(6-{[2-(2-methylphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0355] LCMS: retention time 0.701 min, (Method A); MS (ESI, Pos.): m/z 451.1 (M+H)+;

[0356] ^{1}H NMR (CD_3OD) δ: 7.89, 7.65, 7.57-7.33, 4.72, 4.19-4.03, 3.83, 3.67-3.53, 3.43-3.32, 3.27-3.11, 2.51, 1.89-1.63, 1.56-1.37.

[0357] Example 10: (3S,4R,5R,6S)-1-(6-{[2-(2-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0358] LCMS: retention time 0.704 min, (Method A); MS (ESI, Pos.): m/z 455.1 (M+H)+;

[0359] ^{1}H NMR (CD_3OD) δ: 8.25, 7.62, 7.58-7.48, 7.41-7.27, 4.71, 4.22-4.06, 3.86, 3.68-3.56, 3.46-3.36, 3.27-3.14, 1.89-1.65, 1.57-1.38.

[0360] Example 11: (3S,4R,5R,6S)-1-{6-[(5-phenyl-2-pyrazinyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0361] LCMS: retention time 0.676 min, (Method A); MS (ESI, Pos.): m/z 432.1 (M+H)+;

[0362] ^{1}H NMR (CD_3OD) δ: 9.05, 8.75, 8.04, 7.64-7.46, 4.72, 3.68-3.57, 3.44-3.37, 2.81, 2.61-2.45, 1.73-1.63, 1.55-1.28.

[0363] Example 12: (3S,4R,5R,6S)-1-(6-{[2-(4-fluorophenyl)-1,3-thiazol-5-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0364] LCMS: retention time 0.739 min, (Method A); MS (ESI, Pos.): m/z 455.2 (M+H)+;

[0365] ^{1}H NMR (D_2O) δ: 7.92-7.86, 7.27, 4.78, 4.08-4.06, 3.72, 3.60, 3.33, 3.20-3.15, 1.70-1.56, 1.35-1.29.

[0366] Example 13: (3S,4R,5R,6S)-1-(6-{[4-(4-fluorophenyl)-1,3-thiazol-2-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0367] LCMS: retention time 0.755 min, (Method A); MS (ESI, Pos.): m/z 455.2 (M+H)+;

[0368] ^{1}H NMR (CD_3OD) δ: 7.94-7.89, 7.75, 7.15, 4.82, 3.65, 3.58-3.56, 3.40-3.37, 2.83, 2.57-2.51, 1.70-1.64, 1.51-1.35.

[0369] Example 14: (3S,4R,5R,6S)-1-(6-{[2-(4-fluorophenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0370] LCMS: retention time 0.731 min, (Method A); MS (ESI, Pos.): m/z 439.2 (M+H)+;

[0371] ^{1}H NMR (D_2O) δ: 7.96-7.88, 7.22, 4.45, 4.07-4.05, 3.74, 3.60-3.50, 3.42-3.23, 3.17-3.12, 1.70-1.53, 1.34-1.30.

[0372] Example 15: (3S,4R,5R,6S)-1-(6-{[2-(4-fluorophenyl)-5-methyl-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0373] LCMS: retention time 0.712 min, (Method A); MS (ESI, Pos.): m/z 469 (M+H)+;

[0374] ^{1}H NMR (D_2O) δ: 7.88-7.73, 7.22, 4.56, 4.08-3.92, 3.70, 3.60-3.50, 3.41-2.99, 2.44, 1.75-1.43, 1.38-1.14.

[0375] Example 16: (3S,4R,5R,6S)-1-{6-[(3'-fluoro-4-biphenylyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0376] LCMS: retention time 0.744 min, (Method A); MS (ESI, Pos.): m/z 448.1 (M+H)+;

[0377] ^{1}H NMR (CD_3CN) δ: 7.63, 7.55-7.36, 7.20-7.05, 4.51, 3.86-3.30, 2.78, 2.50, 1.68-1.51, 1.52-1.24.

[0378] Example 17: (3S,4R,5R,6S)-1-(6-{[3'-(trifluoromethyl)-4-biphenylyl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0379] LCMS: retention time 0.767 min, (Method A); MS (ESI, Pos.): m/z 498.1 (M+H)+;

[0380] ^{1}H NMR ($CDCl_3$) δ: 7.81, 7.73, 7.61-7.48, 7.41, 4.52, 3.70, 3.58, 3.48, 2.88, 2.66-2.46, 1.71-1.18.

[0381] Example 18: (3S,4R,5R,6S)-1-(6-{[4'-(trifluoromethyl)-4-biphenylyl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0382] LCMS: retention time 0.785 min, (Method A); MS (ESI, Pos.): m/z 498.1 (M+H)+;

[0383] ^{1}H NMR ($CDCl_3$) δ: 7.70-7.60, 7.55, 7.40, 4.51, 3.84, 3.69, 3.47, 2.99, 2.84-2.58, 1.69-1.46, 1.43-1.19.

[0384] Example 19: (3S,4R,5R,6S)-1-(6-{[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0385] LCMS: retention time 0.72 min, (Method A); MS (ESI, Pos.): m/z 471 (M+H)+;

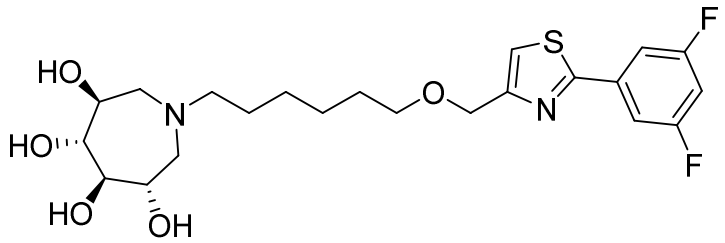
[0386] ^{1}H NMR (CD_3OD) δ: 7.95, 7.56-7.48, 4.66, 3.64-3.55, 3.46-3.38, 2.82, 2.60-2.45, 1.72-1.61, 1.56-1.29.

[0387] Example 20: (3S,4R,5R,6S)-1-(6-{[2-(3,4-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0388] LCMS: retention time 0.707 min, (Method A); MS (ESI, Pos.): m/z 473.1 (M+H)+;

[0389] ^{1}H NMR (CD_3OD) δ: 7.95-7.82, 7.80-7.69, 7.49, 7.45-7.34, 4.63, 3.65-3.52, 3.43-3.36, 2.81, 2.57-2.49, 1.71-1.59, 1.56-1.27.

[0390] Example 21: (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol



[0391] LCMS: retention time 0.709 min, (Method A); MS (ESI, Pos.): m/z 473.1 (M+H)+;

[0392] ^{1}H NMR (CD_3OD) δ: 7.69-7.50, 7.15-7.02, 4.67, 3.68-3.53, 3.46-3.37, 2.90-2.76, 2.58-2.44, 1.70-1.60, 1.56-1.30.

[0393] Example 22: (3S,4R,5R,6S)-1-(6-{[2-(4-methylphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0394] LCMS: retention time 0.71 min, (Method A); MS (ESI, Pos.): m/z 451.1 (M+H)+;

[0395] ^{1}H NMR (CD_3OD) δ: 7.84, 7.42, 7.31, 4.64, 3.70-3.55, 3.44-3.38, 2.82, 2.65-2.47, 2.41, 1.72-1.60, 1.56-1.29.

[0396] Example 23: (3S,4R,5R,6S)-1-(6-{[2-(4-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0397] LCMS: retention time 0.749 min, (Method A); MS (ESI, Pos.): m/z 467.1 (M+H)+;

[0398] ^{1}H NMR (CD_3OD) δ: 7.91, 7.39, 7.06, 4.64, 3.89, 3.68-3.56, 3.44, 2.86, 2.74-2.48, 1.72-1.60, 1.59-1.29.

[0399] Example 24: (3S,4R,5R,6S)-1-(6-{[2-(3,4,5-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0400] LCMS: retention time 0.724 min, (Method A); MS (ESI, Pos.): m/z 491 (M+H)+;

[0401] ^{1}H NMR (CD_3OD) δ: 7.81-7.70, 7.54, 4.64, 3.72, 3.59, 3.48, 2.94, 2.84-2.60, 1.70-1.51, 1.49-1.30.

[0402] Example 25: (3S,4R,5R,6S)-1-(6-{[2-(3-chloro-4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0403] LCMS: retention time 0.725 min, (Method A); MS (ESI, Pos.): m/z 489 (M+H)+;

[0404] ^{1}H NMR (CD_3OD) δ: 8.13, 7.99-7.88, 7.53, 7.40, 4.66, 4.22-4.04, 3.85, 3.69-3.52, 3.47-3.35, 3.29-3.14, 1.91-1.65, 1.55-1.37.

[0405] Example 26: (3S,4R,5R,6S)-1-[6-({2-[4-(trifluoromethoxy)phenyl]-1,3-thiazol-4-yl}methoxy)hexyl]-3,4,5,6-azepanetetrol

[0406] LCMS: retention time 0.746 min, (Method A); MS (ESI, Pos.): m/z 521.1 (M+H)+;

[0407] ^{1}H NMR (CD_3OD) δ: 8.07, 7.50, 7.40, 4.65, 3.66-3.51, 3.40-3.36, 2.78, 2.56-2.50, 1.72-1.58, 1.54-1.26.

[0408] Example 27: (3S,4R,5R,6S)-1-(6-{[2-(3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0409] LCMS: retention time 0.696 min, (Method A); MS (ESI, Pos.): m/z 467.1 (M+H)+;

[0410] ^{1}H NMR (CD_3OD) δ: 7.54-7.46, 7.39, 7.04, 4.58, 3.85, 3.61-3.55, 3.46, 2.78, 2.50-2.42, 1.63-1.54, 1.47-1.24.

[0411] Example 28: (3S,4R,5R,6S)-1-[6-(3-biphenylylmethoxy)hexyl]-3,4,5,6-azepanetetrol

[0412] LCMS: retention time 0.726 min, (Method A); MS (ESI, Pos.): m/z 430.1 (M+H)+;

[0413] ^{1}H NMR (CD_3OD) δ: 7.65-7.57, 7.54, 7.48-7.39, 7.38-7.28, 4.57, 3.61-3.55, 3.53, 3.41-3.36, 2.80, 2.58-2.46, 1.71-1.58, 1.54-1.29.

[0414] Example 29: (3S,4R,5R,6S)-1-(6-{[4-(1,3-thiazol-4-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0415] LCMS: retention time 0.669 min, (Method A); MS (ESI, Pos.): m/z 437.1 (M+H)+;

[0416] ^{1}H NMR (D_2O) δ: 9.07, 7.88-7.71, 7.40, 4.48, 4.07-3.92, 3.67, 3.60-3.39, 3.37-2.97, 1.72-1.40, 1.35-1.12.

[0417] Example 30: (3S,4R,5R,6S)-1-[6-({2-[3-(trifluoromethoxy)phenyl]-1,3-thiazol-4-yl}methoxy)hexyl]-3,4,5,6-azepanetetrol

[0418] LCMS: retention time 0.721 min, (Method A); MS (ESI, Pos.): m/z 521.1 (M+H)+;

[0419] ^{1}H NMR (CD_3OD) δ: 7.96-7.86, 7.58, 7.52, 7.38, 4.65, 3.65-3.55, 3.43-3.36, 2.82, 2.66-2.45, 1.69-1.60, 1.55-1.46, 1.46-1.38, 1.37-1.29.

[0420] Example 31: 3-{4-[({6-[(3S,4R,5R,6S)-3,4,5,6-tetrahydroxy-1-azepanyl]hexyl}oxy)methyl]-1,3-thiazol-2-yl}benzonitrile

[0421] LCMS: retention time 0.678 min, (Method A); MS (ESI, Pos.): m/z 462.1 (M+H)+;

[0422] ^{1}H NMR (CD_3OD) δ: 8.34, 8.26, 7.83, 7.69, 7.57, 4.67, 3.65-3.53, 3.43-3.36, 2.80, 2.60-2.46, 1.72-1.61, 1.56-1.25.

[0423] Example 32: 4-{4-[({6-[(3S,4R,5R,6S)-3,4,5,6-tetrahydroxy-1-azepanyl]hexyl}oxy)methyl]-1,3-thiazol-2-yl}benzonitrile

[0424] LCMS: retention time 0.673 min, (Method A); MS (ESI, Pos.): m/z 462.2 (M+H)+;

[0425] ^{1}H NMR (CD_3OD) δ: 8.15, 7.86, 7.60, 4.68, 3.67-3.52, 3.46-3.36, 2.81, 2.64-2.45, 1.71-1.60, 1.57-1.26.

[0426] Example 33: (3S,4R,5R,6S)-1-(6-{[2-(4-fluoro-3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0427] LCMS: retention time 0.703 min, (Method A); MS (ESI, Pos.): m/z 485.1 (M+H)+;

[0428] ^{1}H NMR (CD_3OD) δ: 7.72, 7.51-7.42, 7.19, 4.63, 3.96, 3.65-3.55, 3.44-3.37, 2.83, 2.64-2.49, 1.71-1.58, 1.56-1.27.

[0429] Example 34: (3S,4R,5R,6S)-1-[6-({2-[4-(methylsulfonyl)phenyl]-1,3-thiazol-4-yl}methoxy)hexyl]-3,4,5,6-azepanetetrol

[0430] LCMS: retention time 0.656 min, (Method A); MS (ESI, Pos.): m/z 515 (M+H)+;

[0431] ^{1}H NMR (CD_3OD) δ: 8.25, 8.09, 7.62, 4.70, 3.66-3.55, 3.43-3.38, 3.20, 2.82, 2.62-2.47, 1.72-1.61, 1.56-1.30.

[0432] Example 35: (3S,4R,5R,6S)-1-(6-{[6-(3-fluoro-5-methoxyphenyl)-3-pyridinyl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0433] LCMS: retention time 1.031 min, (Method D); MS (ESI, Pos.): m/z 479.2 (M+H)+;

[0434] ^{1}H NMR (D_2O) δ: 8.74, 8.59, 8.26, 7.32-7.15, 7.05, 4.10, 3.89, 3.86-3.02, 1.84-1.57, 1.46-1.31.

[0435] Example 36: (3S,4R,5R,6S)-1-(6-{[5-(3-fluoro-5-methoxyphenyl)-2-pyridinyl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0436] LCMS: retention time 0.665 min, (Method A); MS (ESI, Pos.): m/z 479.1 (M+H)+;

[0437] ^{1}H NMR (CD_3OD) δ: 8.73, 8.10, 7.61, 7.12-6.94, 6.76, 4.64, 3.87, 3.65-3.52, 3.43-3.35, 2.81, 2.62-2.44, 1.74-1.61, 1.58-1.40, 1.40-1.30.

[0438] Example 37: (3S,4R,5R,6S)-1-(6-{[2-(3-chloro-5-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0439] LCMS: retention time 1.808 min, (Method B); MS (ESI, Pos.): m/z 501.2 (M+H)+;

[0440] ^{1}H NMR (CD_3OD) δ: 7.60-7.50, 7.49, 7.09, 4.67, 3.91, 3.70-3.55, 3.43, 2.85, 2.64-2.53, 1.71-1.65, 1.55-1.36.

[0441] Example 38: (3S,4R,5R,6S)-1-{6-[(2-cyclohexyl-1,3-thiazol-4-yl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0442] LCMS: retention time 0.715 min, (Method A); MS (ESI, Pos.): m/z 443 (M+H)+;

[0443] ^{1}H NMR (CD_3OD) δ: 7.28, 4.53, 3.62-3.52, 3.44-3.37, 3.05-2.95, 2.82, 2.60-2.48, 2.16-2.09, 1.92-1.84, 1.82-1.75, 1.67-1.20.

[0444] Example 39: (3S,4R,5R,6S)-1-{6-[(2-propyl-1,3-thiazol-4-yl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0445] LCMS: retention time 0.655 min, (Method A); MS (ESI, Pos.): m/z 403 (M+H)+;

[0446] ^{1}H NMR (CD_3OD) δ: 7.32, 4.57, 3.68-3.53, 3.45-3.39, 3.01, 2.84, 2.67-2.50, 1.96-1.75, 1.69-1.60, 1.58-1.30, 1.04.

[0447] Example 40: (3S,4R,5R,6S)-1-(6-{[2-(2,4-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0448] LCMS: retention time 0.723 min, (Method A); MS (ESI, Pos.): m/z 473.1 (M+H)+;

[0449] ^{1}H NMR (CD_3OD) δ: 8.28, 7.56, 7.22-7.08, 4.67, 3.61-3.54, 3.42-3.35, 2.80, 2.58-2.48, 1.69-1.60, 1.55-1.46, 1.45-1.37, 1.36-1.29.

[0450] Example 41: (3S,4R,5R,6S)-1-(6-{[2-(2,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0451] LCMS: retention time 0.764 min, (Method A); MS (ESI, Pos.): m/z 473.2 (M+H)+;

[0452] ^{1}H NMR (CD_3OD) δ: 8.02-7.95, 7.63, 7.40-7.35, 7.27-7.20, 4.69, 3.70-3.57, 3.42, 2.92-2.80, 2.69-2.51, 1.70-1.61, 1.66-1.55, 1.48-1.41, 1.39-1.32.

[0453] Example 42: (3S,4R,5R,6S)-1-(6-{[2-(2,6-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0454] LCMS: retention time 0.689 min, (Method A); MS (ESI, Pos.): m/z 473.1 (M+H)+;

[0455] ^{1}H NMR (D_2O) δ: 7.76, 7.57-7.51, 7.20-7.15, 4.69, 4.18-4.02, 3.88-3.53, 3.49-3.10, 1.84-1.53, 1.43-1.24.

[0456] Example 43: (3S,4R,5R,6S)-1-(6-{[2-(2,3,4-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0457] LCMS: retention time 0.78 min, (Method A); MS (ESI, Pos.): m/z 491.2 (M+H)+;

[0458] ^{1}H NMR (CD_3OD) δ: 8.10-8.00, 7.63, 7.35-7.24, 4.68, 3.63-3.51, 3.43-3.34, 2.79, 2.59-2.44, 1.70-1.59, 1.55-1.27.

[0459] Example 44: (3S,4R,5R,6S)-1-(6-{[2-(2,4,6-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0460] LCMS: retention time 0.749 min, (Method A); MS (ESI, Pos.): m/z 491.2 (M+H)+;

[0461] ^{1}H NMR (CD_3OD) δ: 7.71, 7.15-7.04, 4.68, 3.65-3.53, 3.45-3.37, 2.84, 2.63-2.50, 1.66-1.33.

[0462] Example 45: (3S,4R,5R,6S)-1-[6-({2-[(E)-2-phenylvinyl]-1,3-thiazol-4-yl}methoxy)hexyl]-3,4,5,6-azepanetetrol

[0463] LCMS: retention time 1.706 min, (Method B); MS (ESI, Pos.): m/z 463.2 (M+H)+;

[0464] ^{1}H NMR (CD_3OD) δ: 7.64, 7.55-7.48, 7.46-7.35, 4.62, 3.63-3.56, 3.44-3.40, 2.83, 2.60-2.51, 1.70-1.63, 1.57-1.33.

[0465] Example 46: (3S,4R,5R,6S)-1-[6-(2-naphthylmethoxy)hexyl]-3,4,5,6-azepanetetrol

[0466] LCMS: retention time 1.729 min, (Method B); MS (ESI, Pos.): m/z 404.3 (M+H)+;

[0467] ^{1}H NMR (CD_3OD) δ: 7.90-7.79, 7.62-7.35, 4.67, 3.60-3.53, 3.42-3.37, 2.81, 2.58-2.47, 1.70-1.62, 1.54-1.41, 1.37-1.30.

[0468] Example 47: (3S,4R,5R,6S)-1-[6-(2-biphenylylmethoxy)hexyl]-3,4,5,6-azepanetetrol

[0469] LCMS: retention time 1.828 min, (Method B); MS (ESI, Pos.): m/z 430.3 (M+H)+;

[0470] ^{1}H NMR (DMSO-D_6) δ: 7.54-7.51, 7.51-7.33, 7.30-7.23, 4.36, 3.64-3.52, 3.44-3.34, 2.83, 2.63-2.43, 1.59-1.43, 1.38-1.26.

[0471] Example 48: (3S,4R,5R,6S)-1-{6-[(3',5'-difluoro-2-biphenylyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0472] LCMS: retention time 1.89 min, (Method B); MS (ESI, Pos.): m/z 466.3 (M+H)+;

[0473] ^{1}H NMR (CD_3OD) δ: 7.56-7.25, 7.22-6.91, 4.35, 3.63-3.50, 3.45-3.36, 2.80, 2.56-2.49, 1.61-1.44, 1.41-1.26.

[0474] Example 49: (3S,4R,5R,6S)-1-{6-[(3,4-dipropylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0475] LCMS: retention time 2.148 min, (Method B); MS (ESI, Pos.): m/z 438.4 (M+H)+;

[0476] ^{1}H NMR (CD_3OD) δ: 7.15-7.01, 4.43, 3.60-3.53, 3.47, 3.40-3.35, 2.79, 2.63-2.46, 1.64-1.55, 1.52-1.45, 1.42-1.36, 1.34-1.28, 1.02-0.97.

[0477] Example 50: formic acid - (3S,4R,5R,6S)-1-(6-{[2-(3-methylbutyl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol (1:1)

[0478] LCMS: retention time 0.756 min, (Method A); MS (ESI, Pos.): m/z 424.2 (M+H)+;

[0479] ^{1}H NMR (DMSO-D_6) δ: 8.18, 7.37-7.08, 4.44, 3.31-2.99, 2.66, 2.62-2.57, 2.57-2.54, 2.46-2.39, 1.64-1.47, 1.44-1.22, 0.93.

[0480] Example 51: (3S,4R,5R,6S)-1-{6-[(4-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0481] LCMS: retention time 1.854 min, (Method B); MS (ESI, Pos.): m/z 396.4 (M+H)+;

[0482] ^{1}H NMR (CD_3OD) δ: 7.24, 7.17, 4.45, 3.60, 3.48, 3.44-3.37, 2.84, 2.64-2.49, 1.67-1.56, 1.54-1.46, 1.43-1.29, 0.93.

[0483] Example 52: (3S,4R,5R,6S)-1-(6-{[4-(1-cyclohexen-1-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol

[0484] LCMS: retention time 0.781 min, (Method A); MS (ESI, Pos.): m/z 456.2 (M+Na)+;

[0485] ^{1}H NMR ($CDCl_3$) δ: 7.35, 7.26, 6.16-6.05, 4.46, 3.75, 3.60, 3.44, 2.93, 2.76-2.63, 2.63-2.52, 2.41-2.37, 2.22-2.17, 1.81-1.73, 1.69-1.56, 1.54-1.45, 1.38-1.25.

[0486] Example 53: (3S,4R,5R,6S)-1-(6-{[3-(1-cyclohexen-1-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol

[0487] LCMS: retention time 1.996 min, (Method B); MS (ESI, Pos.): m/z 434.4 (M+H)+;

[0488] ^{1}H NMR (CD_3OD) δ: 7.36-7.23, 7.17, 6.11, 4.48, 3.58, 3.49, 3.43-3.35, 2.81, 2.61-2.47, 2.41, 2.28-2.17, 1.86-1.75, 1.74-1.57, 1.55-1.45, 1.43-1.28.

[0489] Example 54: (3S,4R,5R,6S)-1-{6-[(3-cyclohexylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0490] LCMS: retention time 0.865 min, (Method A); MS (ESI, Pos.): m/z 436.3 (M+H)+;

[0491] ^{1}H NMR (CD_3OD) δ: 7.30-7.06, 4.46, 3.65-3.52, 3.52-3.44, 3.43-3.35, 2.83, 2.61-2.44, 1.92-1.80, 1.80-1.71, 1.65-1.56, 1.54-1.27.

[0492] Example 55: (3S,4R,5R,6S)-1-(6-{[2-(1-cyclohexen-1-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol

[0493] LCMS: retention time 0.75 min, (Method A); MS (ESI, Pos.): m/z 434.2 (M+H)+;

[0494] ^{1}H NMR (DMSO-D_6) δ: 7.39-7.32, 7.26-7.18, 7.13-7.05, 5.55-5.49, 4.67, 4.49, 4.37, 3.42-3.36, 3.22-3.13, 2.68-2.59, 2.44-2.34, 2.20-2.07, 1.75-1.57, 1.56-1.46, 1.41-1.18.

[0495] Example 56: (3S,4R,5R,6S)-1-{6-[(2-cyclohexylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0496] LCMS: retention time 0.758 min, (Method A); MS (ESI, Pos.): m/z 436.2 (M+H)+;

[0497] ^{1}H NMR (DMSO-D_6) δ: 7.30-7.22, 7.16-7.09, 4.67, 4.48, 4.45, 3.42, 3.22-3.13, 2.83-2.71, 2.63, 2.43-2.34, 1.81-1.68, 1.58-1.47, 1.47-1.16.

[0498] Example 57: (3S,4R,5R,6S)-1-{6-[(4-cyclohexylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0499] LCMS: retention time 2.08 min, (Method B); MS (ESI, Pos.): m/z 436.4 (M+H)+;

[0500] ^{1}H NMR ($CDCl_3$) δ: 7.26, 7.18, 4.45, 3.80-3.72, 3.64-3.57, 3.45, 2.98-2.90, 2.72-2.56, 2.52-2.45, 1.76-1.72, 1.63-1.56, 1.56-1.42, 1.42-1.28.

[0501] Example 58: (3S,4R,5R,6S)-1-(6-{[3-(3,5-difluorophenyl)-1,2-oxazol-5-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0502] LCMS: retention time 1.69 min, (Method B); MS (ESI, Pos.): m/z 457.4 (M+H)+;

[0503] ^{1}H NMR (DMSO-D_6) δ: 7.68-7.59, 7.43, 7.17, 4.68, 4.64, 4.49, 3.50, 3.39-3.32, 3.21-3.14, 2.69-2.58, 2.44-2.31, 1.59-1.48, 1.42-1.34, 1.33-1.22.

[0504] Example 59: (3S,4R,5R,6S)-1-(6-{[5-(3,5-difluorophenyl)-1,2-oxazol-3-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[0505] LCMS: retention time 0.783 min, (Method A); MS (ESI, Pos.): m/z 457.3 (M+H)+;

[0506] ^{1}H NMR (CD_3OD) δ: 7.53-7.44, 7.15-7.05, 6.96, 4.60, 3.59-3.53, 3.41-3.35, 2.79, 2.56-2.47, 1.68-1.58, 1.56-1.44, 1.44-1.31.

[0507] Example 60: (3S,4R,5R,6S)-1-{6-[(4-ethylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0508] LCMS: retention time 0.708 min, (Method A); MS (ESI, Pos.): m/z 382.1 (M+H)+;

[0509] ^{1}H NMR (CD_3OD) δ: 7.25, 7.19, 4.45, 3.61-3.52, 3.47, 3.43-3.35, 2.80, 2.63, 2.58-2.45, 1.65-1.28, 1.22.

[0510] Reference Example 2: (3S,4R,5R,6S)-1-{6-[(4-bromobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[0511] Titled compound was synthesized according to procedures analogous to Reference Example 1 and Example 1 using (4-bromophenyl) methanol (CAS No. 873-75-6) instead of (4-methylphenyl) methanol.

[0512] LCMS: retention time 0.702 min, (Method A); MS (ESI, Pos.): m/z 431.8, 433.8 $[M+H]^+$.

[0513] Example 61: (3S,4R,5R,6S)-1-(6-{[4-(3,6-dihydro-2H-pyran-4-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol

[0514] To a solution of the compound prepared in Reference Example 2 (150mg) in 1,4-dioxane (2mL) and water (0.5mL) was added K_2CO_3 (144mg), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS No. 287944-16-5, 109mg) and Pd(dppf)Cl_2 (12.7mg) at 20~25℃. The reaction mixture was stirred at 100℃ for 16h to give a brown solution. The reaction mixture was concentrated to dryness. The residue was purified by reversed phase column (30~40% MeCN in water) to afford the titled compound (35mg).

[0515] LCMS: retention time 0.69 min, (Method A); MS (ESI, Pos.): m/z 436.1 (M+H)+;

[0516] ^{1}H NMR (CD_3OD) δ: 7.42, 7.31, 6.25-6.14, 4.48, 4.30, 3.92, 3.59, 3.49, 3.44-3.37, 2.83, 2.65-2.46, 1.66-1.57, 1.66-1.57, 1.45-1.36, 1.36-1.27.

[0517] Example 62 to 67

[0518] Example 62 to 67 were synthesized according to procedures analogous to Example 62 using the compound prepared in Reference Example 2 and the corresponding boronic acid or boronic ester instead of 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

[0519] Example 62: (3S,4R,5R,6S)-1-{6-[(4'-fluoro-4-biphenylyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0520] LCMS: retention time 0.739 min, (Method A); MS (ESI, Pos.): m/z 448.1 (M+H)+;

[0521] ^{1}H NMR ($CDCl_3$) δ: 7.58-7.48, 7.40, 7.12, 4.53, 3.65, 3.59-3.52, 3.49, 2.88, 2.62-2.47, 1.68-1.60, 1.51-1.24.

[0522] Example 63: 4'-[({6-[(3S,4R,5R,6S)-3,4,5,6-tetrahydroxy-1-azepanyl]hexyl}oxy)methyl]-3-biphenylcarbonitrile

[0523] LCMS: retention time 0.716 min, (Method A); MS (ESI, Pos.): m/z 455.1 (M+H)+;

[0524] ^{1}H NMR (CD_3OD) δ: 7.99, 7.95, 7.75-7.58, 7.46, 4.55, 3.63-3.56, 3.52, 3.45-3.31, 2.90-3.75, 2.62-2.45, 1.71-1.59, 1.56-1.45, 1.45-1.39, 1.39-1.28.

[0525] Example 64: (3S,4R,5R,6S)-1-{6-[(4'-fluoro-3'-methoxy-4-biphenylyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0526] LCMS: retention time 0.729 min, (Method A); MS (ESI, Pos.): m/z 478.1 (M+H)+;

[0527] ^{1}H NMR (CD_3OD) δ: 7.59, 7.41, 7.33-7.26, 7.18-7.12, 4.53, 3.94, 3.61, 3.52, 3.46-3.37, 2.85, 2.68-2.49, 1.69-1.58, 1.58-1.46, 1.46-1.28.

[0528] Example 65: 4'-[({6-[(3S,4R,5R,6S)-3,4,5,6-tetrahydroxy-1-azepanyl]hexyl}oxy)methyl]-4-biphenylcarbonitrile

[0529] LCMS: retention time 0.721 min, (Method A); MS (ESI, Pos.): m/z 455.1 (M+H)+;

[0530] ^{1}H NMR (CD_3OD) δ: 7.86-7.77, 7.68, 7.48, 4.56, 3.67, 3.53, 3.45, 2.89, 2.64, 1.69-1.60, 1.55, 1.49-1.39, 1.39-1.30.

[0531] Example 66: 4'-[({6-[(3S,4R,5R,6S)-3,4,5,6-tetrahydroxy-1-azepanyl]hexyl}oxy)methyl]-2-biphenylcarbonitrile

[0532] LCMS: retention time 0.715 min, (Method A); MS (ESI, Pos.): m/z 455.1 (M+H)+;

[0533] ^{1}H NMR (CD_3OD) δ: 7.82, 7.78-7.70, 7.65-7.44, 4.58, 3.62-3.51, 3.44-3.35, 2.82, 2.61-2.45, 1.69-1.58, 1.56-1.47, 1.47-1.39, 1.39-1.25.

[0534] Example 67: (3S,4R,5R,6S)-1-{6-[(3'-fluoro-5'-methoxy-4-biphenylyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0535] LCMS: retention time 0.75 min, (Method A); MS (ESI, Pos.): m/z 478.1 (M+H)+;

[0536] ^{1}H NMR (CD_3OD) δ: 7.60, 7.42, 7.03-6.90, 6.69, 4.54, 3.85, 3.71-3.57, 3.52, 3.43, 2.96-2.79, 2.76-2.50, 1.68-1.59, 1.59-1.49, 1.47-1.39, 1.38-1.28.

[0537] Example 68: (3S,4R,5R,6S)-1-(6-{[4-(tetrahydro-2H-pyran-4-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol

[0538] To a solution of the compound prepared in Example 61 (20mg) in methanol (1mL) was added Pd/C (5mg, wet, 10%) and purged with H_2 (15psi). The reaction was stirred at 20~25℃ for 15h to give a black suspension. The reaction mixture was filtered and the filtrate was concentrated to dryness. The mixture was purified by prep-HPLC (neutral) and was concentrated to afford the title compound (18.2mg).

[0539] LCMS: retention time 0.689 min, (Method A); MS (ESI, Pos.): m/z 438.1 (M+H)+;

[0540] ^{1}H NMR (CD_3OD) δ: 7.28, 7.24, 4.46, 4.08-3.98, 3.66, 3.61-3.52, 3.51-3.40, 2.99-2.84, 2.84-2.74, 2.74-2.48, 1.85-1.71, 1.66-1.47, 1.46-1.26.

[0541] Reference Example 3: methyl 4-phenoxy-2-pyrimidinecarboxylate

[0542] To a solution of 2-chloro-4-phenoxypyrimidine (CAS No. 18214-00-1, 2.0g) in methanol (115mL) and toluene (23mL) was added TEA (4.04mL) and $Pd(dppf)Cl_2$ (708mg). The mixture was heated to 150℃ under CO (3MPa) for 15h. The reaction mixture was filtered, then the filtrate was concentrated in vacuum to give a residue. The residue was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to dryness. The residue was purified by flash column with silica gel (PE to 30% EtOAc in PE) to give the titled compound (1.3g).

[0543] LCMS: retention time 0.689 min, (Method A); MS (ESI, Pos.): m/z 230.9 $[M+H]^+$

[0544] Reference Example 4: (4-phenoxy-2-pyrimidinyl)methanol

[0545] To a mixture of the compound prepared in Reference Example 3 (500mg) in methanol (6mL) was added $NaBH_4$ (98.6mg) at 0℃. The resulting mixture was stirred at 20~25℃ for 2h. The reaction mixture was concentrated in vacuum. The residue was diluted with EtOAc, washed with H_2O and brine, then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the title compound (470mg, crude). The crude product was used for next step directly.

[0546] Reference Example 5: 2-(bromomethyl)-4-phenoxypyrimidine

[0547] To a solution of the compound prepared in Reference Example 4 (150mg) and PPh_3 (292mg) in DCM (2mL) was added CBr_4 (492mg) in DCM (1mL) at 0~5℃. The mixture was refluxed for 6h. The reaction mixture was diluted with DCM, washed with H_2O, and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC (PE/EtOAc=3/1) to give the title compound (100mg).

[0548] ^1H NMR ($CDCl_3$) δ: 8.61-8.53, 7.50-7.42, 7.34-7.28, 7.21-7.15, 6.69, 4.45.

[0549] Reference Example 6: 6-[(4-phenoxy-2-pyrimidinyl)methoxy]-1-hexanol

[0550] To a solution of the compound prepared in Reference Example 5 (150mg) and *t*-BuOK (95mg) in THF (4.5mL) was added hexane-1,6-diol (CAS No. 629-11-8, 0.12mL) dropwise. The mixture was stirred at 20~25℃ for 16h. The reaction mixture was diluted with H_2O and extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-TLC (PE/EtOAc=1/1) to give the title compound (30mg).

[0551] LCMS: retention time 0.756 min, (Method A); MS (ESI, Pos.): m/z 302.9 $[M+H]^+$

[0552] Reference Example 7: 6-[(4-phenoxy-2-pyrimidinyl)methoxy]hexyl 4-methylbenzenesulfonate

[0553] To a solution of the compound prepared in Reference Example 6 (45mg) in DCM (0.64mL) and pyridine (0.010mL) was added TsCl (34mg) at 0~5℃. The mixture was stirred at 20~25℃ for 5h. The reaction mixture was diluted with DCM, washed with H_2O, and extracted with DCM. The combined organic layers were separated, dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-TLC (PE/EtOAc=3/1) to give the title compound (15mg).

[0554] LCMS: retention time 0.956 min, (Method A); MS (ESI, Pos.): m/z 457.0 $[M+H]^+$.

[0555] Example 69: (3S,4R,5R,6S)-1-{6-[(4-phenoxy-2-pyrimidinyl)methoxy]hexyl}-3,4,5,6-azepanetetrol

[0556] To a solution of the compound prepared in Reference Example 7 (15mg) and (3S,4R,5R,6S)-azepane-3,4,5,6-tetrol hydrochloride salt (9.8mg) in DMSO (0.18mL) was added DIEA (0.03mL). The resulting mixture was heated at 80-90℃ for 2h. The mixture was purified by prep-HPLC (base) to give the title compound (6.6mg).

[0557] LCMS: retention time 0.667 min, (Method A); MS (ESI, Pos.): m/z 448 (M+H)+;

[0558] ^1H NMR (CD_3OD) δ: 8.44, 7.35-7.21, 7.02-6.88, 6.79, 5.18, 4.38, 3.71, 3.48, 3.06-2.60, 1.84-1.70, 1.63-1.29.

[0559] Reference Example 8: 1-bromo-2-({[6-(trityloxy)hexyl]oxy}methyl)benzene

[0560] To a mixture of (2-bromophenyl)methanol (CAS No. 18982-54-2, 500mg) in DMF (5mL) was added NaH (160mg, 60% in oil) at 0~5℃. The mixture was stirred at 0~5℃ for 0.5h. Then reaction mixture was added (((6-bromohexyl)oxy)methanetriyl)tribenzene (CAS No. 113354-79-3, 2.3g) and KI (44.3mg) at 0~5℃. The reaction mixture was stirred at 20℃ for 1.5h to give a brown solution. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were washed with water, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column with silica gel (PE to 0% EtOAc in PE) to afford the title compound (1.1g).

[0561] TLC R_f=0.5 (PE/EtOAc=1/1).

[0562] Reference Example 9: 6-[(2-bromobenzyl)oxy]-1-hexanol

[0563] To a solution of the compound prepared in Reference Example 8 (1.1g,) in DCM (12mL) was added formic acid (0.80mL) at 20℃. The mixture was stirred at 20℃ for 17h to give a colorless solution. The reaction mixture was poured into H_2O, extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column with silica gel (PE to 25% EtOAc in PE) to afford the title compound (300mg).

[0564] TLC R_f=0.3 (PE/EtOAc=3/1).

[0565] Reference Example 10: 6-{[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]oxy}-1-hexanol

[0566] To a solution of the compound prepared in Reference Example 9 (300mg) in 1,4-Dioxane (4mL) was added KOAc (308mg), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (531mg) and Pd(dppf)Cl_2 (38.2mg) at 20~25℃. The reaction mixture was stirred at 80℃ for 15h under N_2. The reaction mixture was filtered. The filtrate was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to afford the title compound (300mg).

[0567] LCMS: retention time 0.927 min, (Method A); MS (ESI, Pos.): m/z 357.1 $[M+Na]^+$

[0568] Reference Example 11: 6-{[2-(4,6-difluoro-2-pyridinyl)benzyl]oxy}-1-hexanol

[0569] To a solution of 2-bromo-4,6-difluoropyridine (CAS No. 41404-63-1, 100mg) in 1,4-dioxane (5mL) and water (1mL) were added K_2CO_3 (214mg), the compound prepared in Reference Example 10 (258mg) and Pd(dppf)Cl_2 (37.7mg) at 20~25℃. The reaction mixture was stirred at 80℃ for 4h to give a yellow suspension. The reaction mixture was filtered. The filtrate was poured into water and extracted with EtOAc. The combined organic phases were

washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column with silica gel (PE to 20% EtOAc in PE) to afford the title compound (190mg).

[0570] TLC R_f=0.3 (PE/EtOAc=3/1).

[0571] Reference Example 12: 6-{[2-(4,6-difluoro-2-pyridinyl)benzyl]oxy}hexanal

[0572] To a solution of the compound prepared in Reference Example 11 (190mg) in DCM (4mL) was added DMP (377mg) at 20℃. The reaction mixture was stirred at 20℃ for 1h. The reaction mixture was quenched by sat. $Na_2S_2O_3$aq. and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column with silica gel (PE to 10% EtOAc in PE) to afford the title compound (60.0mg).

[0573] TLC R_f=0.50 (PE/EtOAc=3/1).

[0574] Example 70: (3S,4R,5R,6S)-1-(6-{[2-(4,6-difluoro-2-pyridinyl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol

[0575] To a mixture of the compound prepared in Reference Example 12 (60mg) in methanol (3mL) was added (3S,4R,5R,6S)-azepane-3,4,5,6-tetrol hydrochloride salt (41mg) and NaOAc (73mg) at 20℃. The reaction mixture was stirred at 20℃ for 0.5h to give a yellow solution. Then $NaBH_3CN$ (35mg) was added in the mixture at 20℃. The reaction mixture was stirred at 20℃ for 15h. The reaction mixture was concentrated to dryness. The residue was purified by prep-HPLC (neutral) to afford the title compound (34mg).

[0576] LCMS: retention time 0.693 min, (Method A); MS (ESI, Pos.): m/z 489.1 $(M+Na)^+$;

[0577] ^{1}H NMR (DMSO-D_6) δ: 7.59-7.53, 7.52-7.47, 7.46-7.40, 7.31-7.22, 4.66, 4.57, 4.48, 3.40-3.36, 3.32-3.29, 3.19-3.15, 2.62, 2.37, 1.43-1.29, 1.21-1.13.

[0578] Reference Example 13: 1-[(4-ethoxy-3-fluorobenzyl)oxy]-6-[(triisopropylsilyl)oxy]-2-hexanol

[0579] To a solution of (3-ethoxy-4-fluorophenyl)methanol (CAS No. 1000207-64-6, 800mg) in *t*-BuOH (5mL) was added 15% NaOHaq. (5mL), triisopropyl(4-(oxiran-2-yl)butoxy)silane (CAS No. 2734792-44-8, 1.41g) and TBAI (758mg) at 20~25℃. The resulting mixture was purged with N_2 for 3 times and stirred at 90℃ for 15h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column with silica gel (PE to 15% of EtOAc in PE) to afford the title compound (660mg).

[0580] TLC R_f=0.40 (PE/EtOAc=5/1).

[0581] Reference Example 14: ({6-[(4-ethoxy-3-fluorobenzyl)oxy]-5-fluorohexyl}oxy)(triisopropyl)silane

[0582] To a solution of the compound prepared in Reference Example 13 (660mg) in DCM (1mL) was added DAST (0.26mL) at 0℃. The mixture was stirred for 5min. The mixture was quenched by sat. $NaHCO_3$aq., washed with water, extracted with DCM. The combined organic layers were concentrated and purified by flash column with silica gel (PE to 5% EtOAc in PE,) to give the title compound (160mg).

[0583] TLC R_f=0.60 (PE/EtOAc=10/1).

[0584] Reference Example 15: 6-[(4-ethoxy-3-fluorobenzyl)oxy]-5-fluoro-1-hexanol

[0585] To a mixture of the compound prepared in Reference Example 14 (160mg) in THF (2mL) was added 1M TBAF in THF (0.54mL) at 20℃. The reaction was stirred at 20℃ for 1h to give a yellow solution. The reaction was concentrated to dryness. The residue was directly purified by flash column with silica gel (PE to 35% EtOAc in PE,) to afford the title compound (90mg).

[0586] TLC Rf=0.20 (PE/EtOAc=2/1).

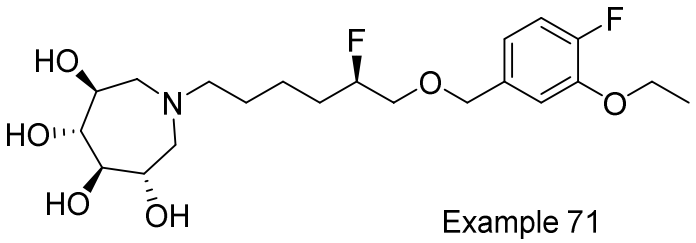
[0587] Reference Example 16: 6-[(4-ethoxy-3-fluorobenzyl)oxy]-5-fluorohexyl 4-methylbenzenesulfonate

[0588] To a solution of the compound prepared in Reference Example 15 (85mg) in DCM (2mL) was added 4-methyl benzene-1-sulfonyl chloride (0.090mL), TEA (0.12mL) and DMAP (13mg,) at 25℃. The reaction mixture was stirred at 25℃ for 15h. The reaction mixture was concentrated to dryness. The residue was purified by flash column with silica gel (PE to 20% EtOAc in PE,) to afford the title compound (100mg).

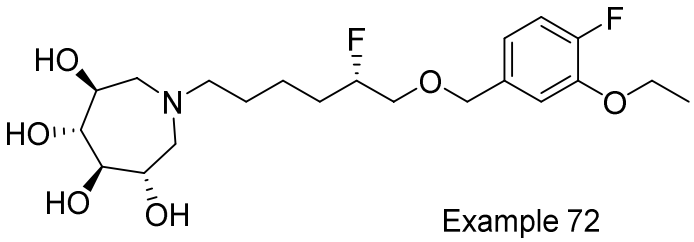
[0589] TLC R_f=0.60 (PE/EtOAc=3/1).

[0590] Example 71: (3S,4R,5R,6S)-1-{(5R)-6-[(3-ethoxy-4-fluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0591] Example 72: (3S,4R,5R,6S)-1-{(5S)-6-[(3-ethoxy-4-fluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)



Example 71



Example 72

[0592] To a solution of (3S,4R,5R,6S)-azepane-3,4,5,6-tetrol hydrochloride salt (68mg) in DMSO (1.5mL) was added DIEA (0.19mL), KI (19mg) and the compound prepared in Reference Example 16 (100mg) at 20~25℃. The reaction mixture was stirred at 80℃ for 2h. The reaction mixture was concentrated to dryness. The residue was purified by prep-HPLC (NH_3) and chiral SFC separation to obtain isomer 1 (5.0mg) and isomer 2 (15mg).

[0593] Example 71 (isomer 1): LCMS: retention time 0.683 min, (Method A); MS (ESI, Pos.): m/z 434.1 (M+H)+;

[0594] ^{1}H NMR (CD_3OD) δ: 7.12-7.00, 6.92-6.84, 4.73-4.65, 4.51, 4.10, 3.67-3.50, 3.43-3.36, 2.81, 2.61-2.47, 1.74-1.35;

[0595] SFC Retention Time: 6.027min (Method: A1).

[0596] Example 72 (isomer 2): LCMS: retention time 0.688 min, (Method A); MS (ESI, Pos.): m/z 434.1 (M+H)+;

[0597] ^{1}H NMR (CD_3OD) δ: 7.13-7.00, 6.92-6.84, 4.75-4.65, 4.51, 4.10, 3.68-3.50, 3.44-3.35, 2.80, 2.59-2.44, 1.74-1.39;

[0598] SFC Retention Time: 6.254min (Method: A1).

[0599] Example 73 to 86

[0600] Example 73 to 86 were synthesized according to procedures analogous to Reference Example 13, 14, 15, 16, Example 71 and 72 using the corresponding alcohol compound instead of (3-ethoxy-4-fluorophenyl)methanol.

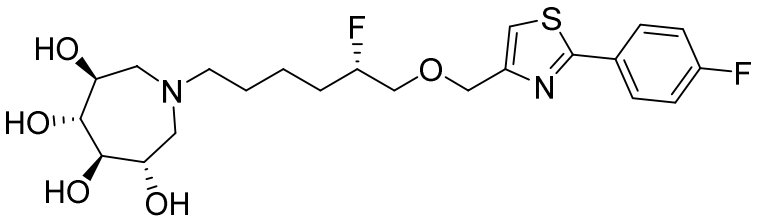
[0601] Example 73: (3S,4R,5R,6S)-1-[(5R)-5-fluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol (isomer 1)

[0602] LCMS: retention time 1.612 min, (Method B); MS (ESI, Pos.): m/z 473.1 (M+H)+;

[0603] ^{1}H NMR (CD_3OD) δ: 7.99, 7.48, 7.26-7.19, 4.75-4.57, 4.72, 3.75-3.65, 3.60-3.52, 3.41-3.37, 2.79, 2.60-2.44, 1.73-1.40;

[0604] SFC Retention Time: 4.734min (Method: B8).

[0605] Example 74: (3S,4R,5R,6S)-1-[(5S)-5-fluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol (isomer 2)



[0606] LCMS: retention time 1.62 min, (Method B); MS (ESI, Pos.): m/z 473.1 (M+H)+;

[0607] ^{1}H NMR (CD_3OD) δ: 8.05-7.95, 7.48, 7.27-7.19, 4.75-4.57, 4.72, 3.78-3.63, 3.45, 2.90, 2.80-2.50, 1.75-1.38;

[0608] SFC Retention Time: 3.393min (Method: B8).

[0609] Example 75: (3S,4R,5R,6S)-1-{5-fluoro-6-[(3,4,5-trifluorobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0610] LCMS: retention time 0.726 min, (Method A); MS (ESI, Pos.): m/z 426.1 (M+H)+;

[0611] ^{1}H NMR (CD_3OD) δ: 7.13-7.10, 4.75-4.60, 4.53, 3.68-3.63, 3.61-3.53, 3.40-3.37, 2.81, 2.58-2.49, 1.74-1.30;

[0612] SFC Retention Time: 1.826min (Method: F4).

[0613] Example 76: (3S,4R,5R,6S)-1-{5-fluoro-6-[(3,4,5-trifluorobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0614] LCMS: retention time 0.741 min, (Method A); MS (ESI, Pos.): m/z 426.1 (M+H)+;

[0615] ^{1}H NMR (CD_3OD) δ: 7.13-7.10, 4.75-4.60, 4.53, 3.71-3.53, 3.41-3.37, 2.81, 2.60-2.49, 1.73-1.51, 1.51-1.37;

[0616] SFC Retention Time: 1.965min (Method: F4).

[0617] Example 77: (3S,4R,5R,6S)-1-[6-(benzyloxy)-5-fluorohexyl]-3,4,5,6-azepanetetrol (isomer 1)

[0618] LCMS: retention time 1.384 min, (Method B); MS (ESI, Pos.): m/z 372.1 (M+H)+;

[0619] ^{1}H NMR (CD_3OD) δ: 7.42-7.21, 4.72-4.55, 4.55, 3.68-3.50, 3.42-3.35, 2.81, 2.59-2.46, 1.73-1.28;

[0620] SFC Retention Time: 6.251min (Method: B5).

[0621] Example 78: (3S,4R,5R,6S)-1-[6-(benzyloxy)-5-fluorohexyl]-3,4,5,6-azepanetetrol (isomer 2)

[0622] LCMS: retention time 1.394 min, (Method B); MS (ESI, Pos.): m/z 372.1 (M+H)+;

[0623] ^{1}H NMR (CD_3OD) δ: 7.39-7.23, 4.72-4.55, 4.56, 3.66-3.51, 3.43-3.35, 2.80, 2.58-2.47, 1.73-1.33;

[0624] SFC Retention Time: 6.795min (Method: B5).

[0625] Example 79: (3S,4R,5R,6S)-1-{5-fluoro-6-[(4-fluorobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0626] LCMS: retention time 1.448 min, (Method B); MS (ESI, Pos.): m/z 390.1 (M+H)+;

[0627] ^{1}H NMR (CD_3OD) δ: 7.37, 7.07, 4.72-4.55, 3.67-3.51, 3.43-3.36, 2.80, 2.59-2.47, 1.75-1.36;

[0628] SFC Retention Time: 6.3min (Method: B4).

[0629] Example 80: (3S,4R,5R,6S)-1-{5-fluoro-6-[(4-fluorobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0630] LCMS: retention time 0.666 min, (Method A); MS (ESI, Pos.): m/z 390 (M+H)+;

[0631] ^{1}H NMR (CD_3OD) δ: 7.37, 7.07, 4.73-4.60, 4.53, 3.66-3.49, 3.44-3.35, 2.80, 2.59-2.46, 1.72-1.37;

[0632] SFC Retention Time: 6.799min (Method: B4).

[0633] Example 81: (3S,4R,5R,6S)-1-{6-[(2-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0634] LCMS: retention time 0.696 min, (Method A); MS (ESI, Pos.): m/z 406.1 (M+H)+;

[0635] ^{1}H NMR ($CDCl_3$) δ: 7.47, 7.39-7.33, 7.31-7.28, 7.25-7.20, 4.78-4.55, 4.66, 3.72-3.65, 3.65-3.61, 3.61-3.50, 2.91, 2.66-2.52, 1.55-1.41;

[0636] SFC Retention Time: 4.572min (Method: G1).

[0637] Example 82: (3S,4R,5R,6S)-1-{6-[(2-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0638] LCMS: retention time 0.694 min, (Method A); MS (ESI, Pos.): m/z 406 (M+H)+;

[0639] ^{1}H NMR ($CDCl_3$) δ: 7.52-7.45, 7.40-7.32, 7.31-7.28, 7.25-7.18, 4.77-4.56, 4.67, 3.73-3.58, 3.58-3.50, 2.91, 2.64-2.49, 1.58-1.35;

[0640] SFC Retention Time: 4.809min (Method: G1).

[0641] Example 83: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(1-propyn-1-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol (isomer 1)

[0642] LCMS: retention time 0.687 min, (Method A); MS (ESI, Pos.): m/z 410.1 (M+H)+;

[0643] ^{1}H NMR ($CDCl_3$) δ: 7.47-7.35, 7.32-7.27, 7.24-7.17, 4.82-4.55, 4.72, 3.72-3.48, 2.87, 2.64-2.49, 2.09, 1.73-1.65, 1.54-1.39;

[0644] SFC Retention Time: 4.628min (Method: G1).

[0645] Example 84: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(1-propyn-1-yl)benzyl]oxy}hexyl)-3,4,5,6-azepanetetrol (isomer 2)

[0646] LCMS: retention time 0.693 min, (Method A); MS (ESI, Pos.): m/z 410.1 (M+H)+;

[0647] ^{1}H NMR ($CDCl_3$) δ: 7.46-7.36, 7.32-7.26, 7.23-7.17, 4.77-4.56, 4.74, 3.69-3.52, 2.87, 2.62-2.50, 2.08, 1.75-1.65, 1.50-1.30;

[0648] SFC Retention Time: 4.865min (Method: G1).

[0649] Example 85: (3S,4R,5R,6S)-1-{6-[(2-chloro-4-methylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0650] LCMS: retention time 0.707 min, (Method A); MS (ESI, Pos.): m/z 420.1 (M+H)+;

[0651] ^{1}H NMR (CD_3OD) δ: 7.36, 7.22, 7.12, 4.73-4.50, 4.59, 3.71-3.52, 3.44-3.34, 2.81, 2.62-2.47, 2.33, 1.73-1.27;

[0652] SFC Retention Time: 1.855min (Method: G2).

[0653] Example 86: (3S,4R,5R,6S)-1-{6-[(2-chloro-4-methylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0654] LCMS: retention time 0.703 min, (Method A); MS (ESI, Pos.): m/z 420.1 (M+H)+;

[0655] ^{1}H NMR (CD_3OD) δ: 7.36, 7.22, 7.13, 4.73-4.50, 4.58, 3.69-3.54, 3.42-3.36, 2.81, 2.61-2.45, 2.33, 1.74-1.28;

[0656] SFC Retention Time: 2.103min (Method: G2).

[0657] Example 87 to 98

[0658] Example 87 to 98 were synthesized according to procedures analogous to Reference Example 13, 14, 15, 16 and Example 69 using the corresponding alcohol compound instead of (3-ethoxy-4-fluorophenyl)methanol.

[0659] Example 87: (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (mixture of two isomer)

[0660] LCMS: retention time 0.711 min, (Method A); MS (ESI, Pos.): m/z 491.1 (M+H)+;

[0661] ^{1}H NMR (DMSO-D_6) δ: 7.75, 7.68-7.60, 7.45-7.36, 4.77-4.67, 4.66, 4.65-4.58, 4.49, 3.76-3.58, 3.37, 3.19, 2.64, 2.44-2.31, 1.65-1.28;

[0662] SFC Retention Time: 3.525/3.851min (Method: B1).

[0663] Example 88: (3S,4R,5R,6S)-1-{6-[(3',5'-difluoro-2-biphenylyl)methoxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (mixture of two isomer)

[0664] LCMS: retention time 1.802 min, (Method B); MS (ESI, Pos.): m/z 484.4 (M+H)+;

[0665] ^{1}H NMR (CD_3OD) δ: 7.66-7.26, 7.19-6.85, 4.70-4.65, 4.57-4.38, 3.67-3.50, 3.43, 2.87, 2.80-2.43, 1.76-1.35;

[0666] SFC Retention Time: 2.082/2.139min (Method: E1).

[0667] Example 89: (3S,4R,5R,6S)-1-(6-{[2-(3-chloro-5-fluorophenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (mixture of two isomer)

[0668] LCMS: retention time 1.793 min, (Method B); MS (ESI, Pos.): m/z 507.4 (M+H)+;

[0669] ^{1}H NMR (CD_3OD) δ: 7.82, 7.72-7.64, 7.57, 7.36-7.29, 4.72, 4.61-4.53, 3.79-3.65, 3.60-3.53, 3.42-3.35, 2.86-2.74, 2.57-2.47, 1.75-1.33.

[0670] Example 90: (3S,4R,5R,6S)-1-(6-{[2-(3-chloro-5-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (mixture of two isomer)

[0671] LCMS: retention time 1.779 min, (Method B); MS (ESI, Pos.): m/z 519.4 (M+H)+;

[0672] ^{1}H NMR (CD_3OD) δ: 7.57-7.49, 7.48-7.42, 7.07, 4.72, 4.59, 3.88, 3.78-3.65, 3.57, 3.43-3.34, 2.80, 2.59-2.44, 1.75-1.32.

[0673] Example 91: (3S,4R,5R,6S)-1-{5-fluoro-6-[(3'-fluoro-2-biphenylyl)methoxy]hexyl}-3,4,5,6-azepanetetrol hydrochloride (1:1) (mixture of two isomer)

[0674] LCMS: retention time 0.735 min, (Method A); MS (ESI, Pos.): m/z 466.2 (M+H)+;

[0675] ^{1}H NMR (CD_3OD) δ: 7.56-7.49, 7.47-7.37, 7.33-7.27, 7.23-7.07, 4.71-4.50, 4.48-4.34, 4.19-4.03, 3.84, 3.65-3.55, 3.54-3.49, 3.41, 3.35, 3.29-3.12, 1.94-1.39;

[0676] SFC Retention Time: 2.298/2.342min (Method: E1).

[0677] Example 92: (3S,4R,5R,6S)-1-{6-[(3',4'-difluoro-2-biphenylyl)methoxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (mixture of two isomer)

[0678] LCMS: retention time 0.743 min, (Method A); MS (ESI, Pos.): m/z 484.1 (M+H)+;

[0679] ^{1}H NMR (DMSO-D_6) δ: 7.55-7.45, 7.45-7.37, 7.32-7.27, 7.24, 4.78-4.43, 4.42-4.32, 3.57-3.42, 3.37, 3.18, 2.64, 2.44-2.29, 1.62-1.24;

[0680] SFC Retention Time: 2.275/2.393min (Method: E1).

[0681] Example 93: (3S,4R,5R,6S)-1-{5-fluoro-6-[(4-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (mixture of two isomer)

[0682] LCMS: retention time 1.789 min, (Method B); MS (ESI, Pos.): m/z 414.2 (M+H)+;

[0683] ^{1}H NMR (CD_3OD) δ: 7.26, 7.17, 4.71-4.50, 4.52, 3.62-3.53, 3.39, 2.82, 2.61-2.50, 1.68-1.37, 0.93.

[0684] Example 94: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(3,4,5-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (mixture of two isomer)

[0685] LCMS: retention time 0.718 min, (Method A); MS (ESI, Pos.): m/z 531.1 (M + Na) (M+H)+;

[0686] ^{1}H NMR (CD_3OD) δ: 7.80-7.71, 7.56, 4.71, 4.60-4.56, 3.75-3.71, 3.69-3.66, 3.60-3.52, 3.41-3.35, 2.79, 2.57-2.49, 1.74-1.58, 1.55-1.40;

[0687] SFC Retention Time: 3.254/3.307min (Method: J1).

[0688] Example 95: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(2,3,4-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (mixture of two isomer)

[0689] LCMS: retention time 0.734 min, (Method A); MS (ESI, Pos.): m/z 531.1 (M + Na) (M+H)+;

[0690] ^{1}H NMR (CD_3OD) δ: 8.09-8.00, 7.66, 7.35-7.22, 4.75, 4.63-4.56, 3.79-3.65, 3.65-3.55, 3.46-3.37, 2.84, 2.67-2.48, 1.76-1.35;

[0691] SFC Retention Time: 2.657/2.747min (Method: E1).

[0692] Example 96: (3S,4R,5R,6S)-1-(6-{[5-(3,5-difluorophenyl)-1,2-oxazol-3-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (mixture of two isomer)

[0693] LCMS: retention time 0.799 min, (Method A); MS (ESI, Pos.): m/z 475.2 (M+H)+;

[0694] ^{1}H NMR ($CDCl_3$) δ: 7.33-7.27, 6.95-6.81, 6.65, 4.80-4.51, 4.70, 3.76, 3.69-3.53, 2.94, 2.81-2.47, 1.83-1.32.

[0695] Example 97: (3S,4R,5R,6S)-1-{5-fluoro-6-[(5-methyl-2-propyl-1,3-thiazol-4-yl)methoxy]hexyl}-3,4,5,6-azepanetetrol (mixture of two isomer)

[0696] LCMS: retention time 1.531 min, (Method B); MS (ESI, Pos.): m/z 435.2 (M+H)+;

[0697] ^{1}H NMR (DMSO-D_6) δ: 4.82-4.50, 4.50-4.34, 3.60-3.37, 3.21-3.14, 2.82, 2.69-2.59, 2.44-2.31, 1.67, 1.59-1.19, 0.92;

[0698] SFC Retention Time: 3.529/3.618min (Method: D1).

[0699] Example 98: (3S,4R,5R,6S)-1-{5-fluoro-6-[(4-isopropylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (mixture of two isomer)

[0700] LCMS: retention time 1.811 min, (Method B); MS (ESI, Pos.): m/z 414.2 (M+H)+;

[0701] ^{1}H NMR (DMSO-D_6) δ: 7.27-7.19, 4.71, 4.62-4.36, 3.63-3.41, 3.19, 2.94-2.80, 2.69-2.60, 2.52-2.51, 2.46-2.30, 1.66-1.28, 1.19;

[0702] SFC Retention Time: 4.438/4.795min (Method: B2).

[0703] Reference Example 17: 2-fluoro-6-[(triisopropylsilyl)oxy]hexanal

[0704] A solution of NFSI (90g) and DL-proline (33g) in THF (560mL) and IPA (70mL) was stirred at 20°C for 15min. Then a solution of 6-((triisopropylsilyl)oxy)hexanal (CAS No. 245124-09-8, 78g) in THF (100mL) was added. The mixture was stirred at 20°C for 16h. To the reaction mixture was added MTBE. The mixture was stirred at -78°C for 30min, then filtered. The filtrate was washed with sat. $NaHCO_3$aq. and brine, dried over Na_2SO_4 and concentrated to give the title compound (78g)), which was used in the next step without any further purification.

[0705] Reference Example 18: 2-fluoro-6-[(triisopropylsilyl)oxy]-1-hexanol

[0706] To a solution of the compound prepared in Reference Example 17 (39g) in DCM (400mL) and EtOH (400mL) was added $NaBH_4$ (28g) at 0℃. The mixture was stirred at 0℃ for 0.5h. The reaction mixture was quenched by sat. NH_4Cl aq. (500mL) at 0℃. The mixture was stirred vigorously for 0.5h. The mixture was extracted with DCM, washed with sat. $NaHCO_3$aq.. The combined organic layers were concentrated to give the crude product. Two batches of crude product were combined and purified by column chromatography with silica gel (EtOAc in PE=0~4%) to give the title compound (30g).

[0707] ^{1}H NMR (CD_3OD) δ: 4.58-4.38, 3.77-3.65, 1.84-1.62, 1.56-1.33, 109-1.04.

[0708] Reference Example 19: methyl 5-(3,5-difluorophenyl)-2-methyl-1,3-oxazole-4-carboxylate

[0709] Titled compound was synthesized according to procedures analogous to Reference Example 11 using methyl 5-bromo-2-methyloxazole-4-carboxylate (CAS No. 1935479-67-6) and (3,5-difluorophenyl)boronic acid (CAS No. 156545-07-2) and was used in the next step without any further purification.

[0710] Reference Example 20: [5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methanol

[0711] To a solution of the compound prepared in Reference Example 19 (5.00g) in THF (200mL) was added 3.5M Red-Al in toluene (7mL) at 0℃. The mixture was stirred at 0℃ for 15min. 1M HClaq. was added to quench the reaction, the mixture was stirred for 10min. The mixture was washed with water and extracted with EtOAc. The water phase was washed with sat NaCl aq. and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. The crude product (5.00g x 6 batches) was purified by column chromatography with silica gel (PE to 28% EtOAc in PE) to give the title compound (14.5 g).

[0712] TLC R_f=0.40 (PE/EtOAc=1/1)

[0713] Reference Example 21: 4-(bromomethyl)-5-(3,5-difluorophenyl)-2-methyl-1,3-oxazole

[0714] A mixture of the compound prepared in Reference Example 20 (12g) in DCM (150mL) was heated to dissolve. After the mixture was cooled, DIEA (19mL) and LiBr (14g) were added to the mixture at 0℃. The mixture was stirred at 0℃ for 10min. Then Ms_2O (12g) was added and the mixture was stirred at 30℃ for 1h. The mixture was washed with water and extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column with silica gel (PE to 10% EtOAc in PE,) to give the title compound (12g).

[0715] TLC R_f=0.70 (PE/EtOAc=3/1).

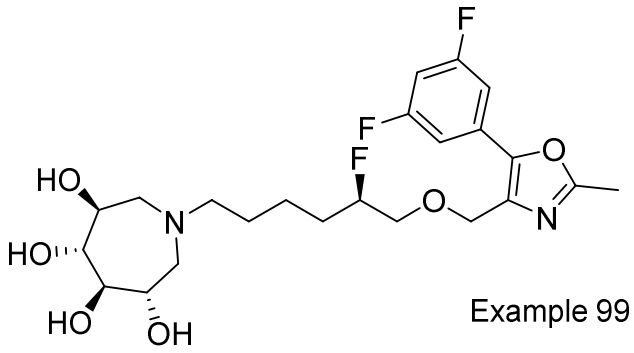
[0716] Reference Example 22: 5-(3,5-difluorophenyl)-4-[({2-fluoro-6-[(triisopropylsilyl)oxy]hexyl}oxy)methyl]-2-methyl-1,3-oxazole

[0717] To a solution of the compound prepared in Reference Example 18 (17g) in THF (300mL) was added NaH (4.7 g, 60% in oil) at 0℃. The mixture was stirred at 0℃ for 30 min. The compound prepared in Reference Example 21 (17g) was added and the mixture was stirred at 0℃ for 16h. The mixture was washed with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica column (PE to 5% EtOAc in PE,) to give the title compound (22g).

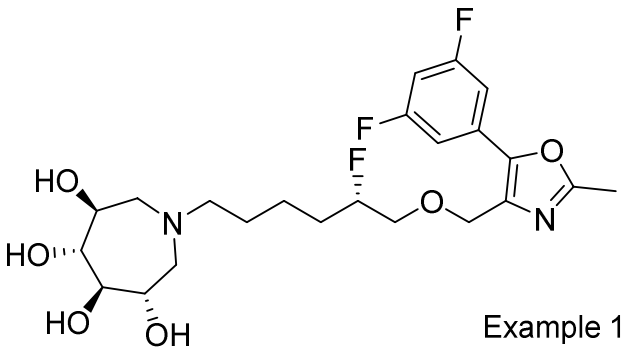
[0718] TLC R_f=0.8 (PE/EtOAc=3/1)

[0719] Example 99: (3S,4R,5R,6S)-1-[(5R)-6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol (isomer 1)

[0720] Example 100: (3S,4R,5R,6S)-1-[(5S)-6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol (isomer 2)



Example 99



Example 100

[0721] Titled compounds were synthesized according to procedures analogous to Reference Example 15, 16, Example 71 and 72 using the compound prepared in Reference Example 22 instead of the compound prepared in Reference Example 14.

[0722] Example 99 (isomer 1): LCMS: retention time 0.681 min, (Method A); MS (ESI, Pos.): m/z 489.1 (M+H)+;

[0723] ^{1}H NMR (CD_3OD) δ: 7.40-7.27, 7.05-6.95, 4.73-4.55, 4.60, 3.76-3.53, 3.43-3.35, 2.79, 2.57-2.45, 1.73-1.33;

[0724] SFC Retention Time: 3.312min (Method: A2).

[0725] Example 100 (isomer 2): LCMS: retention time 0.688 min, (Method A); MS (ESI, Pos.): m/z 489.1 (M+H)+;

[0726] ^{1}H NMR (CD_3OD) δ: 7.40-7.27, 7.05-6.95, 4.73-4.55, 4.60, 3.76-3.53, 3.43-3.35, 2.79, 2.57-2.45, 1.73-1.33;

[0727] SFC Retention Time: 4.893min (Method: A2).

[0728] Reference Example 23: 1-[(4-ethylbenzyl)oxy]-6-[(triisopropylsilyl)oxy]-2-hexanol

[0729] To a solution of (4-ethylphenyl)methanol (CAS No. 768-59-2, 66g) and triisopropyl(4-(oxiran-2-yl)butoxy)silane (158g) in t-BuOH (150mL) was added TBAI (31g) and 15% NaOHaq. (150mL) at 20℃. The reaction was stirred at 80℃ for 16h. The mixture was extracted with EtOAc, washed with brine. The organic phase was concentrated and purified by flash column with silica gel (EtOAc in PE=0~3%) to give the title compound (34g).

[0730] ^{1}H NMR ($CDCl_3$) δ: 7.26, 7.20-7.16, 4.52, 3.86-3.75, 3.68, 3.52-3.47, 3.31, 2.65, 1.49-1.38, 1.28-1.18, 1.06-1.04.

[0731] Reference Example 24: 6-[(4-ethylbenzyl)oxy]-1,5-hexanediol

[0732] To a solution of the compound prepared in Reference Example 23 (60g) in THF (400mL) was added TBAF (152mL) at 20℃. The reaction was stirred at 20℃ for 15h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column with silica gel (EtOAc in PE=55~65%) to give the title compound (30g).

[0733] ^{1}H NMR ($CDCl_3$) δ: 7.26-7.22, 7.20-7.16, 4.51, 3.86-3.76, 3.61, 3.48, 3.31, 2.64, 1.63-1.51, 1.48-1.37, 1.26-1.20.

[0734] Reference Example 25: 6-[(4-ethylbenzyl)oxy]-5-hydroxyhexyl 4-methylbenzenesulfonate

[0735] To a solution of the compound prepared in Reference Example 24 in DCM (400mL) was added TsCl (33g) and TEA (72mL) at 0℃. The mixture was stirred at 20℃ for 16h. The mixture was washed with water and extracted by DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica column chromatography (PE to 35% EtOAc in PE) to give the title compound (33g).

[0736] ^{1}H NMR ($CDCl_3$) δ: 7.77, 7.35-7.29, 7.25-7.21, 7.20-7.15, 4.49, 4.01, 3.76-3.67, 3.43, 3.27, 2.64, 2.44-2.42, 1.71-1.59, 1.42-1.31, 1.23.

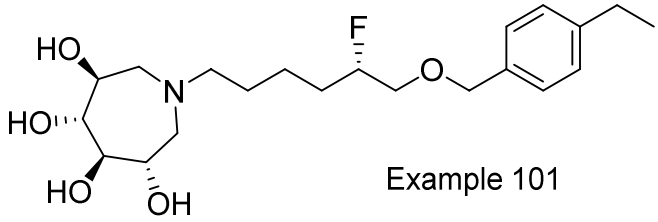
[0737] Reference Example 26: 6-[(4-ethylbenzyl)oxy]-5-fluorohexyl 4-methylbenzenesulfonate

[0738] To a solution of the compound prepared in Reference Example 25 (39g) in THF (400mL) was added PBSF (33mL), hydrogen fluoride in triethylamine (31mL) and TEA (80mL) at 0℃. The reaction was stirred for 16h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column with silica gel (PE to 4% EtOAc in PE) to afford the title compound (12g).

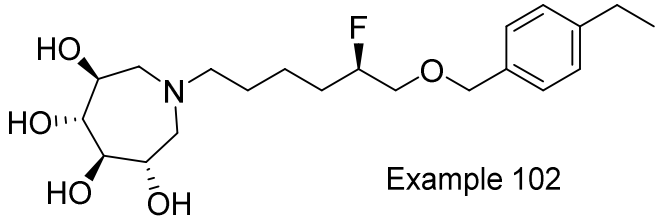
[0739] ^{1}H NMR ($CDCl_3$) δ: 7.78, 7.34, 7.26 (s, 2H), 7.21-7.17, 4.64, 4.55-4.48, 4.03, 3.57-3.47, 2.65, 2.44, 1.73-1.63, 1.56-1.33, 1.23.

[0740] Example 101: (3S,4R,5R,6S)-1-{(5S)-6-[(4-ethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0741] Example 102: (3S,4R,5R,6S)-1-{(5R)-6-[(4-ethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)



Example 101



Example 102

[0742] To a solution of the compound prepared in Reference Example 26 (16g) in DMF (150mL) was added (3S,4R,5R,6S)-azepane-3,4,5,6-tetrol hydrochloride salt (9.5g), KI (12g) and DIEA (33mL) at 25℃. The reaction mixture was stirred at 80℃ for 15h. The mixture was treated with $NaHCO_3$ and extracted by EtOAc. The combined organic layers were washed with water. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude product of titled compounds (14g). The crude products (36g) from two batches was purified by SFC to give the title compound (isomer 1, 14g) and the title compound (isomer 2, 14g).

[0743] Example 101 (isomer 1): LCMS: retention time 0.697 min, (Method A); MS (ESI, Pos.): m/z 400.1 (M+H)+;

[0744] ^{1}H NMR (CD_3OD) δ: 7.26, 7.20, 4.70-4.54, 4.52, 3.61-3.51, 3.43-3.36, 2.80, 2.67-2.59, 2.59-2.45, 1.73-1.31, 1.22;

[0745] SFC Retention Time: 2.827min (Method: B6).

[0746] Example 102 (isomer 2): LCMS: retention time 0.691 min, (Method A); MS (ESI, Pos.): m/z 400.1 (M+H)+;

[0747] ^{1}H NMR (CD_3OD) δ: 7.26, 7.20, 4.73-4.54, 4.52, 3.67-3.51, 3.48-3.37, 2.89-2.68, 2.67-2.48, 1.76-1.56, 1.56-1.32, 1.22;

[0748] SFC Retention Time: 3.852min (Method: B6).

[0749] Example 103 to 134

[0750] Example 103 to 134 were synthesized according to procedures analogous to Reference Example 23, 24, 25, 26, Example 71 and 72 using the corresponding alcohol compound instead of (4-ethylphenyl)methanol.

[0751] Example 103: (3S,4R,5R,6S)-1-[(5R)-5-fluoro-6-{[2-(3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol (isomer 1)

[0752] LCMS: retention time 0.715 min, (Method A); MS (ESI, Pos.): m/z 485.1 (M+H)+;

[0753] ^{1}H NMR (CD_3OD) δ: 7.56-7.44, 7.38, 7.04, 4.71, 4.75-4.56, 3.87, 3.77-3.64, 3.60-3.51, 3.41-3.35, 2.79, 2.58-2.44, 1.74-1.34;

[0754] SFC Retention Time: 5.341min (Method: B7).

[0755] Example 104: (3S,4R,5R,6S)-1-[(5S)-5-fluoro-6-{[2-(3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol (isomer 2)

[0756] LCMS: retention time 0.711 min, (Method A); MS (ESI, Pos.): m/z 485.1 (M+H)+;

[0757] ^{1}H NMR (CD_3OD) δ: 7.54-7.46, 7.38, 7.06-7.01, 4.71, 4.75-4.59, 3.87, 3.76-3.66, 3.60-3.52, 3.42-3.35, 2.79, 2.60-2.42, 1.75-1.60, 1.57-1.34;

[0758] SFC Retention Time: 6.714min (Method: B7).

[0759] Example 105: (3S,4R,5R,6S)-1-(6-{[2-(3,4-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (isomer 1)

[0760] LCMS: retention time 1.665 min, (Method B); MS (ESI, Pos.): m/z 491.1 (M+H)+;

[0761] ^{1}H NMR (CD_3OD) δ: 7.95-7.88, 7.81-7.72, 7.53, 7.45-7.35, 4.71, 4.62-4.59, 3.76-3.72, 3.69-3.65, 3.59, 3.40-3.35, 2.82, 2.63-2.50, 1.78-1.34;

[0762] SFC Retention Time: 2.95min (Method: E1).

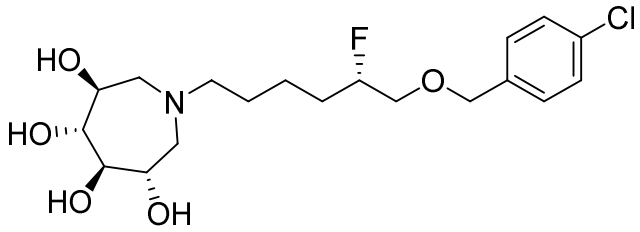
[0763] Example 106: (3S,4R,5R,6S)-1-(6-{[2-(3,4-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (isomer 2)

[0764] LCMS: retention time 1.658 min, (Method B); MS (ESI, Pos.): m/z 491.1 (M+H)+;

[0765] ^{1}H NMR (CD_3OD) δ: 7.95-7.88, 7.80-7.75, 7.53, 7.41-7.33, 4.71, 4.62-4.59, 3.76-3.72, 3.69-3.66, 3.61-3.54, 3.39, 2.81, 2.59-2.49, 1.75-1.49;

[0766] SFC Retention Time: 2.858min (Method: E1).

[0767] Example 107: (3S,4R,5R,6S)-1-{(5S)-6-[(4-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)



[0768] LCMS: retention time 0.694 min, (Method A); MS (ESI, Pos.): m/z 406.1 (M+H)+;

[0769] ^{1}H NMR ($CDCl_3$) δ: 7.36-7.29, 4.78-4.60, 4.55, 3.71, 3.63-3.51, 2.91, 2.69-2.53, 1.59-1.27;

[0770] SFC Retention Time: 2.686min (Method: F4).

[0771] Example 108: (3S,4R,5R,6S)-1-{(5R)-6-[(4-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0772] LCMS: retention time 0.696 min, (Method A); MS (ESI, Pos.): m/z 406.1 (M+H)+;

[0773] ^{1}H NMR ($CDCl_3$) δ: 7.37-7.29, 4.77-4.60, 4.56, 3.71, 3.64-3.50, 2.92, 2.69-2.52, 1.59-1.37;

[0774] SFC Retention Time: 2.973min (Method: F4).

[0775] Example 109: (3S,4R,5R,6S)-1-{6-[(3,4-difluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0776] LCMS: retention time 0.676 min, (Method A); MS (ESI, Pos.): m/z 430.1 (M+Na)+;

[0777] ^{1}H NMR (CD_3OD) δ: 7.31-7.18, 7.16-7.08, 4.74-4.60, 4.53, 3.67-3.62, 3.62-3.51, 3.44-3.35, 2.82, 2.62-2.45, 1.81-1.22;

[0778] SFC Retention Time: 2.01min (Method: F4).

[0779] Example 110: (3S,4R,5R,6S)-1-{6-[(3,4-difluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0780] LCMS: retention time 0.672 min, (Method A); MS (ESI, Pos.): m/z 430 (M+Na)+;

[0781] ^{1}H NMR (CD_3OD) δ: 7.31-7.19, 7.17-7.09, 4.74-4.60, 4.53, 3.66-3.62, 3.60-3.52, 3.43-3.35, 2.80, 2.60-2.44, 1.73-1.39;

[0782] SFC Retention Time: 2.15min (Method: F4).

[0783] Example 111: (3S,4R,5R,6S)-1-{6-[(3-ethoxybenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0784] LCMS: retention time 1.536 min, (Method B); MS (ESI, Pos.): m/z 416.2 (M+H)+;

[0785] ^{1}H NMR (CD_3OD) δ: 7.24, 6.94-6.87, 6.85-6.79, 4.72-4.50, 4.53, 4.03, 3.63-3.53, 3.41-3.37, 2.80, 2.59-2.47, 1.72-1.43, 1.38;

[0786] SFC Retention Time: 4.762min (Method: G1).

[0787] Example 112: (3S,4R,5R,6S)-1-{6-[(3-ethoxybenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0788] LCMS: retention time 1.534 min, (Method B); MS (ESI, Pos.): m/z 416.1 (M+H)+;

[0789] ^{1}H NMR (CD_3OD) δ: 7.24, 6.94-6.87, 6.85-6.79, 4.73-4.50, 4.53, 4.03, 3.65-3.52, 3.39, 2.81, 2.60-2.46, 1.74-1.42, 1.38;

[0790] SFC Retention Time: 4.577min (Method: G1).

[0791] Example 113: (3S,4R,5R,6S)-1-{6-[(2,4-difluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0792] LCMS: retention time 1.461 min, (Method B); MS (ESI, Pos.): m/z 408.1 (M+H)+;

[0793] ^{1}H NMR (CD_3OD) δ: 7.53-7.42, 7.00-6.91, 4.70-4.60, 4.58, 3.68-3.62, 3.61-3.52, 3.42-3.35, 2.80, 2.60-2.47, 1.75-1.58, 1.56-1.33;

[0794] SFC Retention Time: 4.784min (Method: F5).

[0795] Example 114: (3S,4R,5R,6S)-1-{6-[(2,4-difluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0796] LCMS: retention time 1.47 min, (Method B); MS (ESI, Pos.): m/z 408.1 (M+H)+;

[0797] ^{1}H NMR (CD_3OD) δ: 7.53-7.43, 7.03-6.91, 4.70-4.60, 4.59, 3.68-3.63, 3.61-3.53, 3.42-3.36, 2.80, 2.60-2.48, 1.74-1.58, 1.57-1.38;

[0798] SFC Retention Time: 5.027min (Method: F5).

[0799] Example 115: (3S,4R,5R,6S)-1-{5-fluoro-6-[(2-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0800] LCMS: retention time 0.719 min, (Method A); MS (ESI, Pos.): m/z 414.1 (M+H)+;

[0801] ^{1}H NMR (CD_3OD) δ: 7.31, 7.26-7.12, 4.72-4.50, 3.69-3.51, 3.43-3.35, 2.81, 2.70-2.62, 2.59-2.45, 1.74-1.32, 0.98;

[0802] SFC Retention Time: 2.744min (Method: E1).

[0803] Example 116: (3S,4R,5R,6S)-1-{5-fluoro-6-[(2-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0804] LCMS: retention time 0.721 min, (Method A); MS (ESI, Pos.): m/z 414.1 (M+H)+;

[0805] ^{1}H NMR (CD_3OD) δ: 7.31, 7.25-7.10, 4.71-4.52, 3.68-3.51, 3.43-3.35, 2.81, 2.66, 2.59-2.45, 1.74-1.34, 0.98;

[0806] SFC Retention Time: 2.997min (Method: E1).

[0807] Example 117: (3S,4R,5R,6S)-1-{6-[(4-ethyl-2-methylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0808] LCMS: retention time 0.725 min, (Method A); MS (ESI, Pos.): m/z 414.1 (M+H)+;

[0809] ^{1}H NMR (CD_3OD) δ: 7.18, 7.05-6.95, 4.72-4.63, 4.53, 3.62-3.51, 3.43-3.36, 2.80, 2.63-2.49, 2.32, 1.74-1.60, 1.54-1.34, 1.21;

[0810] SFC Retention Time: 5.967min (Method: B4).

[0811] Example 118: (3S,4R,5R,6S)-1-{6-[(4-ethyl-2-methylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0812] LCMS: retention time 0.73 min, (Method A); MS (ESI, Pos.): m/z 414.1 (M+H)+;

[0813] ^{1}H NMR (CD_3OD) δ: 7.18, 7.05-6.96, 4.71-4.61, 4.53, 3.66-3.52, 3.45-3.36, 2.82, 2.64-2.49, 2.32, 1.72-1.60, 1.55-1.36, 1.21;

[0814] SFC Retention Time: 6.48min (Method: B4).

[0815] Example 119: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(4-methylphenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (isomer 1)

[0816] LCMS: retention time 0.702 min, (Method A); MS (ESI, Pos.): m/z 475.2 (M+Na)+;

[0817] ^{1}H NMR (CD_3OD) δ: 7.92, 7.91, 7.33, 4.73-4.56, 4.54, 3.72-3.67, 3.65-3.62, 3.62-3.54, 3.44-3.37, 2.82, 2.62-2.48, 2.41, 1.70-1.33;

[0818] SFC Retention Time: 4.729min (Method: F1).

[0819] Example 120: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(4-methylphenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (isomer 2)

[0820] LCMS: retention time 0.697 min, (Method A); MS (ESI, Pos.): m/z 475.1 (M+Na)+;

[0821] ^{1}H NMR (CD_3OD) δ: 7.92, 7.91, 7.33, 4.73-4.56, 4.55, 3.73-3.63, 3.62-3.54, 3.45-3.38, 2.83, 2.63-2.51, 2.41, 1.70-1.35;

[0822] SFC Retention Time: 6.14min (Method: F1).

[0823] Example 121: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(4-fluorophenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (isomer 1)

[0824] LCMS: retention time 0.677 min, (Method A); MS (ESI, Pos.): m/z 457.1 (M+H)+;

[0825] ^{1}H NMR (CD_3OD) δ: 8.07, 7.95, 7.28-7.23, 4.74-4.60, 4.57, 3.73-3.68, 3.66-3.62, 3.60-3.53, 3.41-3.36, 2.79, 2.58-2.44, 1.74-1.60, 1.57-1.46;

[0826] SFC Retention Time: 5.91min (Method: F3).

[0827] Example 122: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(4-fluorophenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (isomer 2)

[0828] LCMS: retention time 0.689 min, (Method A); MS (ESI, Pos.): m/z 457.1 (M+H)+;

[0829] ^{1}H NMR (CD_3OD) δ: 8.08, 7.95, 7.28-7.23, 4.73-4.60, 4.56, 3.72-3.68, 3.66-3.62, 3.59-3.52, 3.40-3.36, 2.79, 2.57-2.47, 1.73-1.63, 1.55-1.32;

[0830] SFC Retention Time: 6.763min (Method: F3).

[0831] Example 123: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(3-fluorophenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (isomer 1)

[0832] LCMS: retention time 0.689 min, (Method A); MS (ESI, Pos.): m/z 457.1 (M+H)+;

[0833] ^{1}H NMR (CD_3OD) δ: 7.98, 7.86, 7.79-7.70, 7.59-7.50, 7.31-7.22, 4.75-4.60, 4.58, 3.73-3.69, 3.67-3.63, 3.60-3.51, 3.41-3.37, 2.80, 2.58-2.48, 1.75-1.58, 1.56-1.34;

[0834] SFC Retention Time: 1.704min (Method: F2).

[0835] Example 124: (3S,4R,5R,6S)-1-(5-fluoro-6-{[2-(3-fluorophenyl)-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol (isomer 2)

[0836] LCMS: retention time 0.687 min, (Method A); MS (ESI, Pos.): m/z 457.1 (M+H)+;

[0837] ^{1}H NMR (CD_3OD) δ: 7.98, 7.86, 7.79-7.73, 7.59-7.50, 7.30-7.22, 4.73-4.60, 4.58, 3.73-3.69, 3.66-3.63, 3.60-3.52, 3.40-3.37, 2.80, 2.57-2.47, 1.74-1.62, 1.57-1.36;

[0838] SFC Retention Time: 2.442min (Method: F2).

[0839] Example 125: (3S,4R,5R,6S)-1-{6-[(4-butylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0840] LCMS: retention time 0.757 min, (Method A); MS (ESI, Pos.): m/z 428.2 (M+H)+;

[0841] ^{1}H NMR (CD_3OD) δ: 7.25, 7.17, 4.72-4.63, 4.52, 3.63-3.51, 3.42-3.35, 2.80, 2.64-2.47, 1.71-1.49, 1.47-1.27, 0.94;

[0842] SFC Retention Time: 0.8min (Method: B7).

[0843] Example 126: (3S,4R,5R,6S)-1-{6-[(4-butylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0844] LCMS: retention time 4.203 min, (Method C); MS (ESI, Pos.): m/z 428.2 (M+H)+;

[0845] ^{1}H NMR (CD_3OD) δ: 7.24, 7.16, 4.73-4.53, 4.52, 3.69-3.53, 3.46-3.39, 2.88, 2.70-2.55, 1.72-1.51, 1.48-1.29, 0.94;

[0846] SFC Retention Time: 1.292min (Method: B7).

[0847] Example 127: (3S,4R,5R,6S)-1-{5-fluoro-6-[(2-fluoro-4-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0848] LCMS: retention time 1.8 min, (Method B); MS (ESI, Pos.): m/z 432.2 (M+H)+;

[0849] ^{1}H NMR (CD_3OD) δ: 7.32, 7.00, 6.94, 4.73-4.55, 4.58, 3.65-3.50, 3.50-3.52, 3.41-3.37, 2.89-2.76, 2.63-2.48, 1.67-1.38, 0.94;

[0850] SFC Retention Time: 3.093min (Method: A3).

[0851] Example 128: (3S,4R,5R,6S)-1-{5-fluoro-6-[(2-fluoro-4-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0852] LCMS: retention time 1.793 min, (Method B); MS (ESI, Pos.): m/z 432.1 (M+H)+;

[0853] ^{1}H NMR (CD_3OD) δ: 7.32, 7.00, 6.93, 4.72-4.55, 4.58, 3.65-3.52, 3.44-3.36, 2.86-2.75, 2.63-2.45, 1.71-1.55, 1.55-1.35, 0.94;

[0854] SFC Retention Time: 3.485min (Method: A3).

[0855] Example 129: (3S,4R,5R,6S)-1-{5-fluoro-6-[(2-methyl-4-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0856] LCMS: retention time 0.755 min, (Method A); MS (ESI, Pos.): m/z 428.2 (M+H)+;

[0857] ^{1}H NMR (CD_3OD) δ: 7.21-7.15, 7.02-6.94, 4.75-4.67, 4.58-4.49, 3.71-3.50, 3.46-3.36, 2.84, 2.65-2.49, 2.32, 1.73-1.30, 0.92;

[0858] SFC Retention Time: 5.982min (Method: B4).

[0859] Example 130: (3S,4R,5R,6S)-1-{5-fluoro-6-[(2-methyl-4-propylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0860] LCMS: retention time 0.75 min, (Method A); MS (ESI, Pos.): m/z 428.1 (M+H)+;

[0861] ^{1}H NMR (CD_3OD) δ: 7.17, 7.03-6.91, 4.70-4.62, 4.57-4.49, 3.68-3.51, 3.45-3.37, 2.85, 2.68-2.47, 2.31, 1.68-1.33, 0.92;

[0862] SFC Retention Time: 6.677min (Method: B4).

[0863] Example 131: (3S,4R,5R,6S)-1-{6-[(2,6-difluoro-4-propylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0864] LCMS: retention time 0.749 min, (Method A); MS (ESI, Pos.): m/z 450.1 (M+H)+;

[0865] ^{1}H NMR (CD_3OD) δ: 6.84, 4.60, 4.63-4.47, 3.67-3.51, 3.45-3.35, 2.83, 2.64-2.46, 1.72-1.32, 0.94;

[0866] SFC Retention Time: 6.545min (Method: A3).

[0867] Example 132: (3S,4R,5R,6S)-1-{6-[(2,6-difluoro-4-propylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0868] LCMS: retention time 0.753 min, (Method A); MS (ESI, Pos.): m/z 450.1 (M+H)+;

[0869] ^{1}H NMR (CD_3OD) δ: 6.85, 4.61, 4.63-4.48, 3.68-3.52, 3.44-3.36, 2.83, 2.65-2.50, 1.70-1.57, 1.55-1.31, 0.95;

[0870] SFC Retention Time: 6.945min (Method: A3).

[0871] Example 133: (3S,4R,5R,6S)-1-{6-[(2,4-dimethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 1)

[0872] LCMS: retention time 1.601 min, (Method B); MS (ESI, Pos.): m/z 400.2 (M+H)+;

[0873] ^{1}H NMR (CD_3OD) δ: 7.15, 7.00, 6.96, 4.69-4.50, 3.63-3.51, 3.40-3.36, 2.80, 2.59-2.42, 2.30, 2.28, 1.73-1.29;

[0874] SFC Retention Time: 4.069min (Method: H1).

[0875] Example 134: (3S,4R,5R,6S)-1-{6-[(2,4-dimethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0876] LCMS: retention time 1.597 min, (Method B); MS (ESI, Pos.): m/z 400.2 (M+H)+;

[0877] ^{1}H NMR (CD_3OD) δ: 7.15, 7.00, 6.96, 4.70-4.52, 3.64-3.56, 3.56-3.53, 3.46-3.37, 2.84, 2.59-2.42, 2.30, 1.76-1.32;

[0878] SFC Retention Time: 4.58min (Method: H1).

[0879] Reference Example 27: 1-[(4-methylbenzyl)oxy]-6-[(triisopropylsilyl)oxy]-2-hexanol

[0880] To a solution of (4-methylphenyl)methanol (50g) in t-BuOH (250mL) were added 15% NaOHaq. (250mL) and triisopropyl(4-(oxiran-2-yl)butoxy)silane (123g) and TBAI (66g) at 20℃. The reaction was stirred at 90℃ for 15h. The mixture was poured into water and extracted with EtOAc. The organic phase was concentrated and purified by flash column with silica gel (PE to 5% EtOAc in PE) to give the title compound (79.5g).

[0881] TLC R_f=0.40 (PE/EtOAc=5/1)

[0882] Reference Example 28: 6-[(4-methylbenzyl)oxy]-1,5-hexanediol

[0883] To a solution of the compound prepared in Reference Example 27 (79.5g) in THF (250mL) was added 1M TBAF in THF (292mL) at 20℃. The reaction was stirred at 20℃ for 1h. The reaction mixture was concentrated and the residue was purified by flash column with silica gel (PE to 35% EtOAc in PE) to give the title compound (44.7g).

[0884] TLC R_f=0.20 (PE/EtOAc=2/1)

[0885] Reference Example 29: 5-hydroxy-6-[(4-methylbenzyl)oxy]hexyl 4-methylbenzenesulfonate

[0886] To a solution of the compound prepared in Reference Example 28 (44.7g) in DCM (400mL) was added TsCl (36.3g) and TEA (52.3mL) at 0℃. The mixture was stirred at 20℃

for 16h. The reaction mixture was concentrated and the residue was purified by flash column with silica gel (PE to 20% EtOAc in PE) to give the title compound (45.4g).

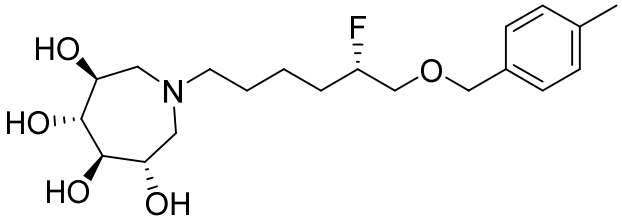
[0887] TLC R_f=0.60 (PE/EtOAc=3/1)

[0888] Reference Example 30: 5-fluoro-6-[(4-methylbenzyl)oxy]hexyl 4-methylbenzenesulfonate

[0889] To a solution of the compound prepared in Reference Example 29 (45.4g) in THF (450mL) was added PBSF (39.9mL), hydrogen fluoride in triethylamine (37.7mL) and TEA (53.1mL) at 0℃. The reaction was stirred at 20℃ for 16h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column with silica gel (PE to 4% EtOAc in PE) to afford the title compound (22.7g).

[0890] TLC R_f=0.50 (PE/EtOAc=5/1)

[0891] Example 135: (3S,4R,5R,6S)-1-{(5S)-5-fluoro-6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 1)



[0892] Example 136: (3S,4R,5R,6S)-1-{(5R)-5-fluoro-6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol (isomer 2)

[0893] To a solution of (3S,4R,5R,6S)-azepane-3,4,5,6-tetrol hydrochloride salt (700mg) in DMF (5mL) were added DIEA (5.5mL), KI (53mg) and the compound prepared in Reference Example 30 (1.25g) at 20~25℃. The reaction mixture was stirred at 80℃ for 16h. The mixture was treated with sat. $NaHCO_3$aq. and extracted by EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by C-18 reversed phase column (10~30% MeCN in water) and chiral SFC separation to obtain isomer 1 (403mg) and isomer 2 (358mg).

[0894] Example 135 (isomer 1): LCMS: retention time 1.514 min, (Method B); MS (ESI, Pos.): m/z 386.1 (M+H)+;

[0895] ^{1}H NMR (CD_3OD) δ: 7.22, 7.16, 4.70-4.51, 4.50, 3.61-3.50, 3.41-3.37, 2.80, 2.60-2.48, 2.33, 1.75-1.58, 1.57-1.31;

[0896] SFC Retention Time: 3.123min (Method: B3).

[0897] Example 136 (isomer 2): LCMS: retention time 1.495 min, (Method B); MS (ESI, Pos.): m/z 386.2 (M+H)+;

[0898] ^{1}H NMR (CD_3OD) δ: 7.22, 7.16, 4.70-4.51, 4.50, 3.64-3.55, 3.44-3.37, 2.83, 2.64-2.48, 2.33, 1.73-1.57, 1.56-1.32;

[0899] SFC Retention Time: 3.884min (Method: B3).

[0900] Reference Example 31: methyl 2-(3,5-difluorophenyl)-1,3-oxazole-4-carboxylate

[0901] To the mixture of methyl 2-amino-3-hydroxypropanoate hydrochloride (CAS No. 5680-80-8, 500mg) and 3,5-difluorobenzaldehyde (CAS No. 32085-88-4, 460mg) in DMA (10mL) was added K_2CO_3 (888mg), the reaction was stirred at 25℃ for 16h. To the reaction mixture was added $BrCCl_3$ (1.9g) and DBU (1.4mL) at 0℃, the reaction was stirred at 25℃ for 16h. The mixture was purified by flash column with silica gel (EtOAc in PE=0~40%,) to give the title compound (390mg).

[0902] TLC R_f=0.50 (EtOAc/PE=1/3).

[0903] Reference Example 32: [2-(3,5-difluorophenyl)-1,3-oxazol-4-yl]methanol

[0904] To a solution of the compound prepared in Reference Example 31 (100mg) in THF (3mL) was added $LiAlH_4$ (20mg) at 0℃, the reaction was stirred at 0℃ for 3h to give a yellow solution. The reaction mixture was quenched by water, 15% NaOHaq. and water. The mixture was dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash column with silica gel (EtOAc in PE=0~50%,) to give the title compound (74mg).

[0905] TLC R_f=0.30 (EtOAc/PE=1/3).

[0906] Example 137 and 138

[0907] Example 137 and 138 were synthesized according to procedures analogous to Reference Example 23, 24, 25, 26, Example 71 and 72 using the corresponding alcohol prepared in Reference example 32 instead of (4-ethylphenyl)methanol.

[0908] Example 137: (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (isomer 1)

[0909] LCMS: retention time 0.778 min, (Method A); MS (ESI, Pos.): m/z 475.2 (M+H)+;

[0910] ^{1}H NMR (CD_3OD) δ: 8.00, 7.64-7.56, 7.22-7.06, 4.74-4.69, 4.59, 3.77-3.51, 3.47-3.35, 2.83, 2.69-2.44, 1.76-1.35;

[0911] SFC Retention Time: 2.37min (Method: F2).

[0912] Example 138: (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl)-3,4,5,6-azepanetetrol (isomer 2)

[0913] LCMS: retention time 0.781 min, (Method A); MS (ESI, Pos.): m/z 475.2 (M+H)+;

[0914] ^{1}H NMR (CD_3OD) δ: 8.00, 7.66-7.49, 7.19-7.05, 4.74-4.65, 4.59, 3.76-3.49, 3.42-3.34, 2.79, 2.58-2.43, 1.75-1.34;

[0915] SFC Retention Time: 3.083min (Method: F2).

[0916] Reference Example 33: methyl 6-(3,5-difluorophenyl)-3-pyridazinecarboxylate

[0917] To a solution of methyl 6-chloropyridazine-3-carboxylate (CAS No. 65202-50-8, 25g) and (3,5-difluorophenyl)boronic acid (32g) in DMF (250mL) was added K_3PO_4 (40g) and Pd(dppf)Cl_2 (1.1g) under N_2. The mixture was stirred at 70℃ for 12h under N_2. The mixture was cooled to 20℃, poured into water and filtered. The filter cake was washed with water. The filtrate was triturated with MeOH and dried in vacuo to give the title compound (10g), which was used in the next step without any further purification.

[0918] Reference Example 34: [6-(3,5-difluorophenyl)-3-pyridazinyl]methanol

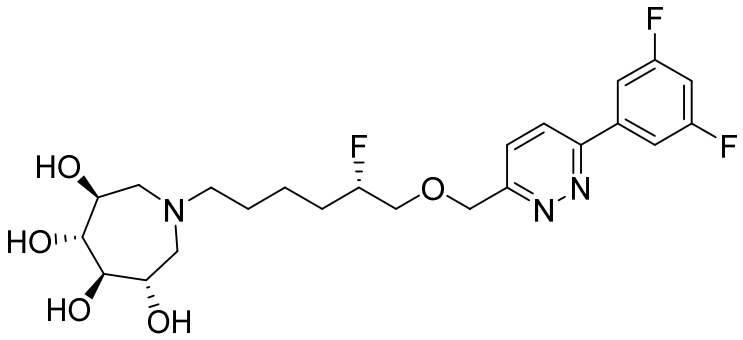
[0919] To a mixture of the compound prepared in Reference Example 33 (4.2g) in THF (80mL) was added $CaCl_2$ (1.9g) and $NaBH_4$ (0.95g) at 0℃. The reaction mixture was stirred at 10℃ for 0.5h and followed by addition of MeOH (4mL) dropwise at 0℃. The mixture was allowed to stirred at 10℃ for 2h to give a yellow solution. The reaction mixture was acidified with 1M HClaq. to pH=8. Water and EtOAc was added to the mixture. The resulting mixture was filtered. The filtrate was extracted with EtOAc. The combined organic phase were washed brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column with silica gel (0%~40% EtOAc in PE,) to give the title compound (2.3g).

[0920] TLC R_f=0.10 (PE/EtOAc=2/1).

[0921] Example 139 and 140

[0922] Example 139 and 140 were synthesized according to procedures analogous to Reference Example 23, 24, 25, 26, Example 71 and 72 using the corresponding alcohol prepared in Reference example 34 instead of (4-ethylphenyl)methanol.

[0923] Example 139: (3S,4R,5R,6S)-1-[(5S)-6-{[6-(3,5-difluorophenyl)-3-pyridazinyl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol (isomer 1)



[0924] LCMS: retention time 0.658 min, (Method A); MS (ESI, Pos.): m/z 486.1 (M+H)+;

[0925] ^{1}H NMR (CD_3OD) δ: 8.25, 7.92, 7.82-7.71, 7.19-7.08, 4.94, 4.80-4.63, 3.85-3.70, 3.60-3.52, 3.43-3.36, 2.81, 2.59-2.49, 1.76-1.42;

[0926] SFC Retention Time: 1.838min (Method: F6).

[0927] Example 140: (3S,4R,5R,6S)-1-[(5R)-6-{[6-(3,5-difluorophenyl)-3-pyridazinyl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol (isomer 2)

[0928] LCMS: retention time 0.662 min, (Method A); MS (ESI, Pos.): m/z 486.1 (M+H)+;

[0929] ^{1}H NMR (CD_3OD) δ: 8.25, 7.93, 7.82-7.71, 7.19-7.08, 4.94, 4.79-4.63, 3.89-3.68, 3.60-3.52, 3.43-3.36, 2.81, 2.62-2.44, 1.76-1.35;

[0930] SFC Retention Time: 3.359min (Method: F6).

[0931] Reference Example 35: (3*E*)-6-(4-biphenylylmethoxy)-3-hexen-1-ol

[0932] To a solution of 4-(bromomethyl)-1,1'-biphenyl (CAS No. 2567-29-5, 250mg) in THF (3mL) and H_2O (0.6mL) was added TBAB (33mg), sat. NaOH aq. (0.28mL) and (*E*)-hex-3-ene-1,6-diol (CAS No. 71655-17-9, 141mg) at 20~25℃, the reaction was stirred at 60℃ for 15h to give a yellow solution. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was directly purified by flash column with silica gel (PE to 15% EtOAc in PE) to afford the title compound (130mg).

[0933] ^{1}H NMR ($CDCl_3$) δ: 7.62-7.56, 7.47-7.38, 7.37-7.32, 5.65-5.55, 5.54-5.45, 4.56, 3.64, 3.54, 2.42-2.34, 2.29.

[0934] Example 141: (3S,4R,5R,6S)-1-[(3E)-6-(4-biphenylylmethoxy)-3-hexen-1-yl]-3,4,5,6-azepanetetrol

[0935] Example 141 was synthesized according to procedures analogous to Reference Example 7 and Example 69 using the corresponding alcohol prepared in Reference example 35 instead of the compound prepared in Reference Example 6.

[0936] LCMS: retention time 0.725 min, (Method A); MS (ESI, Pos.): m/z 428.1 (M+H)+;

[0937] ^{1}H NMR (DMSO-D_6) δ: 7.68-7.62, 7.50-7.43, 7.40, 7.38-7.33, 5.49-5.44, 4.68, 4.50, 3.45, 3.40-3.34, 3.21-3.16, 2.67, 2.48-2.38, 2.29-2.21, 2.14-2.05.

[0938] Example 142 to 146

[0939] Example 142 to 146 were synthesized according to procedures analogous to Reference Example 7 and Example 69 using the corresponding alcohol instead of the compound prepared in Reference Example 6.

[0940] Example 142: (3S,4R,5R,6S)-1-[(3E)-6-{[2-(2,3,4-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}-3-hexen-1-yl]-3,4,5,6-azepanetetrol

[0941] LCMS: retention time 1.705 min, (Method B); MS (ESI, Pos.): m/z 489.1 (M+H)+;

[0942] ^{1}H NMR (CD_3OD) δ: 8.16-7.93, 7.63, 7.36-7.21, 5.59-5.46, 4.70, 3.63-3.52, 3.41-3.34, 2.81, 2.59-2.51, 2.36-2.29, 2.23-2.15.

[0943] Example 143: (3S,4R,5R,6S)-1-{(3E)-6-[(4-propylbenzyl)oxy]-3-hexen-1-yl}-3,4,5,6-azepanetetrol

[0944] LCMS: retention time 1.784 min, (Method B); MS (ESI, Pos.): m/z 394.4 (M+H)+;

[0945] ^{1}H NMR (CD_3OD) δ: 7.24, 7.15, 5.54-5.48, 4.46, 3.59-3.54, 3.48, 3.41-3.37, 2.83, 2.61-2.52, 2.31-2.23, 2.23-2.17, 1.68-1.54, 0.93.

[0946] Example 144: (3S,4R,5R,6S)-1-[(3E)-6-{[2-(3,4-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-3-hexen-1-yl]-3,4,5,6-azepanetetrol

[0947] LCMS: retention time 1.663 min, (Method B); MS (ESI, Pos.): m/z 471.1 (M+H)+;

[0948] ^{1}H NMR (CD_3OD) δ: 7.90-7.86, 7.81-7.72, 7.49, 7.45-7.35, 5.60-5.45, 4.65, 3.65-3.51, 3.42-3.35, 2.82, 2.59-2.52, 2.37-2.27, 2.25-2.14.

[0949] Example 145: (3S,4R,5R,6S)-1-[(3E)-6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-3-hexen-1-yl]-3,4,5,6-azepanetetrol

[0950] LCMS: retention time 1.671 min, (Method B); MS (ESI, Pos.): m/z 471.2 (M+H)+;

[0951] ^{1}H NMR (CD_3OD) δ: 7.70-7.46, 7.19-6.97, 5.57-5.48, 4.66, 3.64-3.53, 3.40-3.37, 2.82, 2.62-2.50, 2.33, 2.25-2.15.

[0952] Example 146: (3S,4R,5R,6S)-1-[(3E)-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}-3-hexen-1-yl]-3,4,5,6-azepanetetrol

[0953] LCMS: retention time 0.68 min, (Method A); MS (ESI, Pos.): m/z 453.1 (M+H)+;

[0954] ^{1}H NMR (DMSO-D_6) δ: 7.98, 7.59, 7.34, 5.46, 4.67, 4.58, 4.49, 3.51, 3.36, 3.20-3.15, 2.66, 2.48-2.37, 2.25, 2.09.

[0955] Reference Example 36: 6-{[2-(2-bromo-1,3-thiazol-4-yl)-2-propanyl]oxy}-1-hexanol

[0956] To a solution of 2-(2-bromo-1,3-thiazol-4-yl)-2-propanol (CAS No. 2228788-36-9, 180mg) in DCM (3mL) were added TsOH (167mg) and 1,6-hexanediol (0.44mL). The mixture was stirred at 50°C for 16h. The reaction mixture was purified by silica gel column chromatography (PE to 18% EtOAc in PE) to give the title compound (48mg).

[0957] TLC R_f=0.2 (PE/EtOAc=3/1).

[0958] Reference Example 37: 6-({2-[2-(1-propyn-1-yl)-1,3-thiazol-4-yl]-2-propanyl}oxy)-1-hexanol

[0959] To a solution of the compound prepared in Reference Example 36 (48mg) in THF (1mL) was added TEA (0.041mL), followed by CuI (1.4mg) and $Pd(PPh_3)_2Cl_2$ (5.2mg). After stirring 5min at 20°C, 1-propyne (1mol/L in THF, 0.89mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at 50°C for 16h. The reaction mixture was diluted with EtOAc (10mL) and filtered. The filtrate was concentrated. The residue was purified by silica gel column chromatography (PE to 20% EtOAc in PE) to give the title compound (25mg).

[0960] TLC R_f=0.2 (PE/EtOAc=2/1).

[0961] Example 147: (3S,4R,5R,6S)-1-[6-({2-[2-(1-propyn-1-yl)-1,3-thiazol-4-yl]-2-propanyl}oxy)hexyl]-3,4,5,6-azepanetetrol

[0962] Example 147 was synthesized according to procedures analogous to Reference Example 16 and Example 69 using the compound prepared in Reference Example 37 instead of the compound prepared in Reference Example 7.

[0963] LCMS: retention time 0.665 min, (Method A); MS (ESI, Pos.): m/z 427.1 (M+H)+;

[0964] ^{1}H NMR (CD_3OD) δ: 7.35, 3.59, 3.40, 3.23, 2.88-2.78, 2.63-2.47, 2.13, 1.55, 1.53-1.44, 1.39 - 1.23.

[0965] Reference Example 38: ethyl [2-(4-chloro-3-fluorophenyl)-1,3-oxazol-4-yl]acetate

[0966] A mixture of 4-chloro-3-fluorobenzamide (CAS No. 874781-07-4, 1.0g) and ethyl 4-chloro-3-oxo-butanoate (CAS No. 638-07-3, 1.9g) was stirred at 140°C for 2h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the residue. The residue was purified by flash column with silica gel (5% EtOAc in PE) to give the title compound (760mg).

[0967] ^{1}H NMR ($CDCl_3$) δ: 7.83-7.70, 7.54-7.41, 4.27-4.18, 3.68, 1.33-1.27.

[0968] Reference Example 39: 2-[2-(4-chloro-3-fluorophenyl)-1,3-oxazol-4-yl]ethanol

[0969] To a solution of the compound prepared in Reference Example 38 (400mg) in THF (4mL) was added $LiAlH_4$ (64mg) at 0°C. The mixture was stirred at 20°C for 1h. The reaction

mixture was quenched by water, and 15% NaOHaq.. The mixture was stirred for 10min. The suspension was diluted with EtOAc filtered and the filter cake was washed with EtOAc. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the title compound (320mg).

[0970] ESI/MS: 241.8 $[M+H]^+$.

[0971] Reference Example 40: 2-(4-chloro-3-fluorophenyl)-4-[2-(4-iodobutoxy)ethyl]-1,3-oxazole

[0972] To a solution of the compound prepared in Reference Example 39 (50mg) in THF (0.50mL) was added 15% NaOHaq. (2.5mL), 1,4-diiodobutane (CAS No. 628-21-7, 0.050mL) and TBAI (67mg) at 20℃, the reaction mixture was stirred at 50℃ for 17h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by prep-TLC (PE/EtOAc=5/1, R_f=0.4) to afford the title compound (25mg).

[0973] TLC R_f=0.40 (PE/EtOAc=5/1).

[0974] Example 148: (3S,4R,5R,6S)-1-(4-{2-[2-(4-chloro-3-fluorophenyl)-1,3-oxazol-4-yl]ethoxy}butyl)-3,4,5,6-azepanetetrol

[0975] Example 148 was synthesized according to procedures analogous to Example 1 using the iodide prepared in Reference Example 40 instead of the compound prepared in Reference Example 1.

[0976] LCMS: retention time 0.69 min, (Method A); MS (ESI, Pos.): m/z 458.9 (M+H)+;

[0977] ^{1}H NMR (CD_3OD) δ: 7.92-7.80, 7.69-7.62, 3.76, 3.63, 3.53, 3.44, 2.88, 2.61, 1.61.

[0978] Example 149 to 153

[0979] Example 149 to 153 were synthesized according to procedures analogous to Reference Example 1 and Example 1 using 1,5-diiodopentane (CAS No. 628-77-3) and corresponding alcohol compounds.

[0980] Example 149: (3S,4R,5R,6S)-1-[5-(4-biphenylylmethoxy)pentyl]-3,4,5,6-azepanetetrol

[0981] LCMS: retention time 1.734 min, (Method B); MS (ESI, Pos.): m/z 416.3 (M+H)+;

[0982] ^{1}H NMR (CD_3OD) δ: 7.61, 7.46-7.40, 7.32, 4.55, 3.61-3.51, 3.43-3.37, 2.81, 2.59-2.48, 1.72-1.61, 1.59-1.48, 1.46-1.37.

[0983] Example 150: (3S,4R,5R,6S)-1-(5-{[4-(4-fluorophenyl)-1,3-thiazol-2-yl]methoxy}pentyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[0984] LCMS: retention time 0.739 min, (Method A); MS (ESI, Pos.): m/z 441.2 (M+H)+;

[0985] ^{1}H NMR (D_2O) δ: 7.81-7.73, 7.19, 4.85, 4.08-4.06, 3.69-3.66, 3.34, 3.23-3.18, 1.73-1.63, 1.62-1.39.

[0986] Example 151: (3S,4R,5R,6S)-1-[5-(3-biphenylylmethoxy)pentyl]-3,4,5,6-azepanetetrol

[0987] LCMS: retention time 0.708 min, (Method A); MS (ESI, Pos.): m/z 416.1 (M+H)+;

[0988] ^{1}H NMR (CD_3OD) δ: 7.63-7.58, 7.54, 7.47-7.40, 7.37-7.29, 4.57, 3.59, 3.54, 3.43-3.38, 2.83, 2.63-2.51, 1.70-1.61, 1.59-1.48, 1.47-1.36.

[0989] Example 152: (3S,4R,5R,6S)-1-(5-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}pentyl)-3,4,5,6-azepanetetrol

[0990] LCMS: retention time 1.632 min, (Method B); MS (ESI, Pos.): m/z 459.2 (M+H)+;

[0991] ^{1}H NMR (CD_3OD) δ: 7.64-7.49, 7.13-7.03, 4.65, 3.64-3.53, 3.42-3.35, 2.82, 2.78, 2.58-2.48, 1.70-1.61, 1.58-1.48, 1.47-1.37.

[0992] Example 153: (3S,4R,5R,6S)-1-[5-(2-biphenylylmethoxy)pentyl]-3,4,5,6-azepanetetrol

[0993] LCMS: retention time 1.736 min, (Method B); MS (ESI, Pos.): m/z 416.3 (M+H)+;

[0994] ^{1}H NMR (CD_3OD) δ: 7.52-7.47, 7.44-7.39, 7.39-7.32, 7.28-7.22, 4.36, 3.60-3.54, 3.41-3.36, 2.80, 2.57-2.47, 1.58-1.43, 1.37-1.28.

[0995] Reference Example 41: 2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethanol

[0996] Titled compound was synthesized according to procedures analogous to Reference Example 39 using ethyl 2-(2-(3,5-difluorophenyl)thiazol-4-yl)acetate (CAS No. 1501541-90-7) instead of the compound prepared in Reference Example 38.

[0997] TLC R_f=0.40 (PE/EtOAc=3/1).

[0998] Example 154: (3S,4R,5R,6S)-1-(5-{2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethoxy}pentyl)-3,4,5,6-azepanetetrol

[0999] Example 154 was synthesized according to procedures analogous to Reference Example 1 and Example 1 using 1,5-diiodopentane and the compound prepared in Reference Example 41.

[01000] LCMS: retention time 0.706 min, (Method A); MS (ESI, Pos.): m/z 473 (M+H)+;

[01001] ^{1}H NMR (DMSO-D_6) δ: 7.64-7.57, 7.51, 7.40-7.32, 4.66, 4.48, 3.71, 3.42-3.37, 3.19-3.14, 2.99, 2.61, 2.40-2.31, 1.52-1.40, 1.40-1.29, 1.28-1.17.

[01002] Example 155 and 156

[01003] Example 155 and 156 were synthesized according to procedures analogous to Reference Example 1 and Example 1 using 1,7-diiodoheptane (CAS No. 51526-03-5) and corresponding alcohol compounds.

[01004] Example 155: (3S,4R,5R,6S)-1-(7-{[4-(4-fluorophenyl)-1,3-thiazol-2-yl]methoxy}heptyl)-3,4,5,6-azepanetetrol

[01005] LCMS: retention time 0.781 min, (Method C); MS (ESI, Pos.): m/z 469.2 (M+H)+;

[01006] ^{1}H NMR (CD_3OD) δ: 7.99-7.90, 7.76, 7.18-7.12, 4.82, 3.64, 3.58-3.57, 3.40-3.38, 2.85-2.72, 2.57-2.50, 1.68-1.64, 1.50-1.33.

[01007] Example 156: (3S,4R,5R,6S)-1-(7-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}heptyl)-3,4,5,6-azepanetetrol

[01008] LCMS: retention time 0.702 min, (Method A); MS (ESI, Pos.): m/z 469.1 (M+H)+;

[01009] ^{1}H NMR (DMSO-D_6) δ: 7.98, 7.58, 7.34, 4.68, 4.56, 4.49, 3.50, 3.45-3.37, 3.24-3.11, 2.75-2.55, 2.47-2.26, 1.62-1.47, 1.44-1.18.

[01010] Example 157: (3S,4R,5R,6S)-1-{4-[(4'-methyl-4-biphenylyl)methoxy]butyl}-3,4,5,6-azepanetetrol

[01011] Example 157 was synthesized according to procedures analogous to Reference Example 1 and Example 1 using 1,4-diiodobutane and corresponding alcohol compounds.

[01012] LCMS: retention time 0.723 min, (Method A); MS (ESI, Pos.): m/z 416.1 (M+H)+;

[01013] ^{1}H NMR ($CDCl_3$) δ: 7.55, 7.48, 7.37, 7.23, 4.51, 3.64, 3.58-3.36, 2.85, 2.66-2.46, 2.38, 2.11-1.70, 1.68-1.48, 1.35-1.23.

[01014] Reference Example 42: methyl 4,4-difluoro-6-hydroxyhexanoate

[01015] To a mixture of 5,5-difluorooxepan-2-one (CAS No. 35196-95-3, 1.7g) in methanol (20mL) was added MeONa (600mg). The reaction mixture was stirred at 25℃ for 16h. The reaction mixture was quenched by sat. NH_4Claq. and extracted with DCM. The combined organic phase were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give the title compound (1.7g), which was used in the next step without any further purification.

[01016] Reference Example 43: methyl 4,4-difluoro-6-[(triisopropylsilyl)oxy]hexanoate

[01017] To a mixture of the compound prepared in Reference Example 42 (0.70g) in DMF (10mL) was added chlorotriisopropylsilane (0.90mL) and imidazole (520mg). The reaction mixture was stirred at 25℃ for 16h to give a brown mixture. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with water, brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated. The residue

was purified by silica gel column chromatography (PE to 10% EtOAc in PE) to give the title compound (0.73g).

[01018] TLC R_f=0.4 (PE/EtOAc=20/1).

[01019] Reference Example 44: 4,4-difluoro-6-[(triisopropylsilyl)oxy]-1-hexanol

[01020] To a mixture of the compound prepared in Reference Example 43 (730mg) in THF (9mL) was added $LiAlH_4$ (123mg). The reaction mixture was stirred at 25℃ for 2h. The reaction mixture was quenched by water, and 15% NaOHaq.. The suspension was diluted with THF and filtered. The filter cake was washed with THF. The filtrate was concentrated in vacuo to give the title compound (640mg), which was used in the next step without any further purification.

[01021] Reference Example 45: [(3,3-difluoro-6-iodohexyl)oxy](triisopropyl)silane

[01022] To a solution of I_2 (785mg) in DCM (8mL) were added PPh_3 (811mg), imidazole (281mg) and the compound prepared in Reference Example 44 (640mg). The reaction mixture was stirred at 25℃ for 16h. The reaction mixture was diluted with DCM and filtered. The filtrate was concentrated in vacuum to give a residue. The residue was purified by silica column chromatography (0~6% EtOAc in PE) to give the title compound (360mg).

[01023] TLC R_f=0.7 (PE/EtOAc=10/1).

[01024] Reference Example 46: 2-(3,5-difluorophenyl)-4-[({4,4-difluoro-6-[(triisopropylsilyl)oxy]hexyl}oxy)methyl]-1,3-thiazole

[01025] To a mixture of [2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methanol (CAS No. 1480594-24-8, 100mg) in DMF (2mL) was added NaH (35mg, 60% in oil) at 0℃. The mixture was stirred at 0℃ for 30min and followed by addition of the compound prepared in Reference Example 45 (222mg). The reaction mixture was stirred at 25℃ for 16h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column with silica gel (0~8% EtOAc in PE) to give the title compound (110mg).

[01026] TLC R_f=0.7 (PE/EtOAc=10/1).

[01027] Example 158: (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-3,3-difluorohexyl)-3,4,5,6-azepanetetrol

[01028] Example 158 was synthesized according to procedures analogous to Reference Example 15, 16 and Example 69 using the compound prepared in Reference Example 46 instead of the compound prepared in Reference Example 14.

[01029] LCMS: retention time 0.732 min, (Method A); MS (ESI, Pos.): m/z 531.1 (M+Na)+;

[01030] ^{1}H NMR (CD_3OD) δ: 7.62-7.53, 7.13-7.04, 4.67, 3.63, 3.58-3.52, 3.38, 2.81, 2.74-2.66, 2.54, 2.14-1.92, 1.87-1.75.

[01031] Example 159 to 161

[01032] Example 159 to 161 were synthesized according to procedures analogous to Reference Example 46, 15, 16 and Example 69 using the corresponding alcohol compounds instead of [2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methanol.

[01033] Example 159: (3S,4R,5R,6S)-1-(6-{[2-(3,4-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-3,3-difluorohexyl)-3,4,5,6-azepanetetrol

[01034] LCMS: retention time 1.724 min, (Method B); MS (ESI, Pos.): m/z 509.1 (M+H)+;

[01035] ^{1}H NMR (CD_3OD) δ: 7.96-7.86, 7.80-7.73, 7.51, 7.44-7.30, 4.65, 3.62, 3.59-3.52, 3.40-3.36, 2.81, 2.75-2.65, 2.54, 2.15-1.90, 1.85-1.75.

[01036] Example 160: (3S,4R,5R,6S)-1-(3,3-difluoro-6-{[2-(2,3,4-trifluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[01037] LCMS: retention time 1.753 min, (Method B); MS (ESI, Pos.): m/z 527.1 (M+H)+;

[01038] ^{1}H NMR (CD_3OD) δ: 8.19-7.91, 7.64, 7.38-7.21, 4.69, 3.63, 3.58-3.52, 3.43-3.34, 2.81, 2.70, 2.59-2.50, 2.13-1.92, 1.86-1.75.

[01039] Example 161: (3S,4R,5R,6S)-1-(3,3-difluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[01040] LCMS: retention time 1.649 min, (Method B); MS (ESI, Pos.): m/z 491.2 (M+H)+;

[01041] ^{1}H NMR (CD_3OD) δ: 8.03-7.95, 7.46, 7.27-7.19, 4.65, 3.62, 3.58-3.50, 3.41-3.36, 2.81, 2.74-2.66, 2.54, 2.14-1.91, 1.85-1.75.

[01042] Reference Example 47: 4,4-difluoro-6-[(triisopropylsilyl)oxy]hexyl benzoate

[01043] To a solution of the compound prepared in Reference Example 44 (15g) in DCM (500mL) was added TEA (10mL), DMAP (590mg), benzoyl chloride (6.7mL) at 0-5℃. The reaction mixture was stirred at 20℃ for 1h to give a yellow solution. The reaction mixture was poured into water and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column with silica gel (EtOAc in PE from 0 to 10%) to afford the title compound (18g).

[01044] ^{1}H NMR ($CDCl_3$) δ: 8.03, 7.56, 7.44, 4.36, 3.89, 2.23-1.91, 1.12-0.99.

[01045] Reference Example 48: 4,4-difluoro-6-hydroxyhexyl benzoate

[01046] To a solution of the compound prepared in Reference Example 47 (15g) in THF (100mL) was added 1M TBAF in THF (54.3mL) at 20℃. The reaction mixture was stirred at

20℃ for 0.5h to give a yellow solution. The reaction mixture was concentrated to dryness. The residue was directly purified by flash column with silica gel (EtOAc in PE from 0 to 50%) to afford the title compound (8.5g).

[01047] ^{1}H NMR ($CDCl_3$) δ: 8.04, 7.57, 7.45, 4.37, 3.89, 2.24-1.99.

[01048] Reference Example 49: 6-[(4-ethylbenzyl)oxy]-4,4-difluoro-1-hexanol

[01049] To a mixture of the compound prepared in Reference Example 48 (93mg) in DMF (2mL) was added NaH (11mg, 60% in oil) at 0℃. The mixture was stirred at 0℃ for 30min and followed by 1-(bromomethyl)-4-ethylbenzene (CAS No. 57825-30-6, 100mg) and TBAI (13mg). The reaction mixture was stirred at 25℃ for 12hr. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and then filtered. The filtration was concentrated. The residue was purified by flash column with silica gel (EtOAc in PE from 0~30%) to give the title compound (60mg).

[01050] ^{1}H NMR ($CDCl_3$) δ: 7.23, 7.20-7.16, 4.47, 3.73-3.58, 2.64, 2.26-2.12, 2.03-1.91, 1.81-1.70, 1.25-1.20, 1.25-1.20.

[01051] Example 162: (3S,4R,5R,6S)-1-{6-[(4-ethylbenzyl)oxy]-4,4-difluorohexyl}-3,4,5,6-azepanetetrol

[01052] Example 162 was synthesized according to procedures analogous to Reference Example 7 and Example 69 using the compound prepared in Reference Example 49 instead of the compound prepared in Reference Example 6.

[01053] LCMS: retention time 1.711 min, (Method B); MS (ESI, Pos.): m/z 418.2 (M+H)+;

[01054] ^{1}H NMR (CD_3CN) δ: 7.26, 7.21, 4.44, 3.63-3.25, 2.85-2.42, 1.93-1.83, 1.67-1.54, 1.20.

[01055] Reference Example 50: 1-{[2-(3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}-6-[(triisopropylsilyl)oxy]-2-hexanol

[01056] To a solution of (2-(3-methoxyphenyl)thiazol-4-yl)methanol (CAS No. 885280-53-5, 500mg) in tert-butanol (5mL) was added 15% NaOHaq. (5mL), TBAI (728mg) and triisopropyl(4-(oxiran-2-yl)butoxy)silane (0.92g) at 20℃. The reaction mixture was stirred at 90℃ for 15h to give a yellow solution. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column with silica gel (PE to 20% EtOAc in PE) to afford the title compound (390mg).

[01057] TLC R_f=0.50 (PE/EtOAc=3/1).

[01058] Reference Example 51: 1-{[2-(3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}-6-[(triisopropylsilyl)oxy]-2-hexanone

[01059] To a solution of the compound prepared in Reference Example 50 (200mg) in DCM (5mL) was added DMP (259mg) at 20℃. The reaction was stirred at 20℃ for 2h. The reaction mixture was poured into sat. $NaHCO_3$aq. and extracted with DCM. The combined organic phases were washed with sat. $NaHCO_3$aq., dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column with silica gel (PE to 15% EtOAc in PE) to afford the title compound (140mg).

[01060] TLC R_f=0.60 (PE/EtOAc=3/1).

[01061] Reference Example 52: 4-[({2,2-difluoro-6-[(triisopropylsilyl)oxy]hexyl}oxy)methyl]-2-(3-methoxyphenyl)-1,3-thiazole

[01062] To a solution of the compound prepared in Reference Example 51 (140mg) in DCM (3mL) was added diethylaminosulfur trifluoride (0.30mL) at 20℃. The reaction mixture was stirred at 35℃ for 15h to give a yellow solution. The reaction was quenched by sat. $NaHCO_3$aq. and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column with silica gel (PE to 8% EtOAc in PE) to afford the title compound (80mg).

[01063] TLC R_f=0.80 (PE/EtOAc=3/1).

[01064] Example 163: (3S,4R,5R,6S)-1-(5,5-difluoro-6-{[2-(3-methoxyphenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol

[01065] Example 163 was synthesized according to procedures analogous to Reference Example 15, 16 and Example 69 using the compound prepared in Reference Example 52 instead of the compound prepared in Reference Example 14.

[01066] LCMS: retention time 0.696 min, (Method A); MS (ESI, Pos.): m/z 503.1 (M+H)+;

[01067] ^{1}H NMR (DMSO-D_6) δ: 7.68, 7.51, 7.45-7.40, 7.09-7.04, 4.71, 4.68, 4.50, 3.83, 3.78, 3.42-3.35, 3.20-3.15, 2.62, 2.41-2.32, 1.98-1.83, 1.39.

[01068] Reference Example 53: 4-[(4-biphenylylmethyl)thio]-1-butanol

[01069] To a solution of 4-(bromomethyl)-1,1'-biphenyl (200mg) and 4-mercapto-1-butanol (CAS No. 14970-83-3, 103mg) in DMF (5mL) was added K_2CO_3 (224mg), the mixture was stirred at 25℃ for 2h. The mixture was diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column with silica gel (EtOAc in PE from 0 to 90%) to afford the title compound (200mg).

[01070] ^{1}H NMR ($CDCl_3$) δ: 7.70-7.52, 7.49-7.32, 3.83-3.73, 3.71-3.58, 2.50, 1.77-1.59.

[01071] Example 164: (3S,4R,5R,6S)-1-{4-[(4-biphenylylmethyl)thio]butyl}-3,4,5,6-azepanetetrol

[01072] Example 164 was synthesized according to procedures analogous to Reference Example 12 and Example 70 using the compound prepared in Reference Example 53 instead of the compound prepared in Reference Example 11.

[01073] LCMS: retention time 0.784 min, (Method A); MS (ESI, Pos.): m/z 418.1 (M+H)+;

[01074] ^{1}H NMR (CD_3OD) δ: 7.62-7.55, 7.45-7.37, 7.36-7.27, 3.75, 3.61-3.49, 3.44-3.35, 2.78, 2.56-2.44, 1.64-1.52.

[01075] Reference Example 54: 4-(2-bromoethyl)-2-(4-fluorophenyl)-1,3-thiazole

[01076] To a solution of 2-(2-(4-fluorophenyl)thiazol-4-yl)ethan-1-ol (CAS No. 871689-11-1, 220mg) in THF (5mL) was added PPh_3 (550mg) and CBr_4 (660mg) at 0℃, the reaction was stirred at 15~20℃ for 5h to give a yellow suspension. The reaction mixture was quenched by water and extracted with EtOAc. The combined organic phase were concentrated to dryness. The residue was purified by flash column with silica gel (EtOAc in PE=0~20%,) and concentrated to give the title compound (260mg).

[01077] TLC R_f=0.70 (PE/EtOAc=3/1).

[01078] Reference Example 55: 4-({2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]ethyl}thio)-1-butanol

[01079] To a solution of the compound prepared in Reference Example 54 (260mg) in DMF (5mL) was added K_2CO_3 (251mg) and 4-mercapto-1-butanol (0.10mL) at 20℃. The resulting mixture was stirred at 15~20℃ for 16h. The reaction mixture was washed with water, extracted with EtOAc. The combined organic layers were concentrated and purified by flash column with silica gel (EtOAc in PE=10~30%) to give the title compound (290mg).

[01080] TLC R_f=0.20 (EtOAc/PE=1/3).

[01081] Reference Example 56: 4-({2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]ethyl}thio)butanal

[01082] To a solution of the compound prepared in Reference Example 55 (100mg) in DMSO (1mL) and DCM (2mL) was added TEA (0.22mL), $Py.SO_3$ (340mg) at 0℃, the reaction was stirred at 0~20℃ for 18h to give a white suspension. The mixture was quenched by water and extracted with EtOAc. The combined organic layer was concentrated and purified by flash column with silica gel (EtOAc in PE=0~20%) to give the title compound (30mg).

[01083] LCMS: retention time 0.898 min, (Method A); MS (ESI, Pos.): m/z 309.9 $[M+H]^+$.

[01084] Example 165: (3S,4R,5R,6S)-1-[4-({2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]ethyl}thio)butyl]-3,4,5,6-azepanetetrol hydrochloride (1:1)

[01085] Example 165 was synthesized according to procedures analogous to Example 70 using the compound prepared in Reference Example 56 instead of the compound prepared in Reference Example 12.

[01086] LCMS: retention time 0.701 min, (Method A); MS (ESI, Pos.): m/z 457 (M+H)+;

[01087] ^{1}H NMR (D_2O) δ: 7.85, 7.46, 7.25, 4.09-3.99, 3.83-3.06, 2.94, 2.53, 1.86-1.66, 1.63-1.52.

[01088] Reference Example 57: S-{2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethyl} ethanethioate

[01089] To a solution of PPh_3 (435mg) in THF (2mL) was added DIAD (0.33mL) at 0-5℃, the reaction was stirred at 0~5℃ for 0.5h to give a white suspension. Then ethanethioic S-acid (CAS No. 507-09-5, 0.12mL) and 2-(2-(3,5-difluorophenyl)thiazol-4-yl)ethan-1-ol (CAS No. 1874632-93-5, 200mg) in THF (1mL) was added in the mixture at 0~5℃. The reaction was stirred at 0~5℃ for 2h, then the reaction was stirred at 20℃ for 15h. The reaction mixture was concentrated to dryness. The residue was purified by preparative TLC (PE/EtOAc =5/1, R_f=0.6) to afford the title compound (240mg).

[01090] TLC Rf=0.60 (PE/EtOAc=5/1).

[01091] Reference Example 58: 5-({2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethyl}thio)-1-pentanol

[01092] To a solution of the compound prepared in Reference Example 54 (100mg) in methanol (1mL) was added K_2CO_3 (138mg) at 20℃. The reaction mixture was stirred at 20℃ for 1h. Then 5-bromopentan-1-ol (CAS No. 34626-51-2. 279mg) was added to the mixture and the mixture was stirred at 20℃ for 2h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was directly purified by flash column with silica gel (PE to 25% EtOAc in PE,) to afford the title compound (70mg).

[01093] TLC R_f=0.30 (PE/EtOAc=3/1).

[01094] Example 166: (3S,4R,5R,6S)-1-[5-({2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethyl}thio)pentyl]-3,4,5,6-azepanetetrol

[01095] Example 166 was synthesized according to procedures analogous to Reference Example 12 and Example 70 using the compound prepared in Reference Example 58 instead of the compound prepared in Reference Example 11.

[01096] LCMS: retention time 0.732 min, (Method A); MS (ESI, Pos.): m/z 489 (M+H)+;

[01097] ^{1}H NMR (DMSO-D_6) δ: 7.61, 7.54, 7.35, 3.55-3.49, 3.39-3.32, 3.21-3.15, 3.04-2.98, 2.91-2.84, 2.65-2.57, 2.40-2.29, 1.55-1.42, 1.40-1.24.

[01098] Reference Example 59: 4-({2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethyl}thio)-1-butanol

[01099] Titled compound was synthesized according to procedures analogous to Reference Example 54 and 55 using the compound prepared in Reference Example 41.

[01100] LCMS: retention time 0.926 min, (Method A); MS (ESI, Pos.): m/z 330.0 $[M+H]^+$.

[01101] Reference Example 60: 2-(3,5-difluorophenyl)-4-{2-[(4-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}butyl)thio]ethyl}-1,3-thiazole

[01102] To a mixture of the compound prepared in Reference Example 59 (120mg) in DMF (4mL) was added tert-butylchlorodimethylsilane (60mg) and imidazole (50mg). The reaction was stirred at 20℃ for 16h to give a colorless solution. The mixture was washed with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica column (PE to 8% EtOAc in PE) to give the title compound (196mg).

[01103] LCMS: retention time 1.264 min, (Method A); MS (ESI, Pos.): m/z 444.1 $[M+H]^+$.

[01104] Reference Example 61: 2-(3,5-difluorophenyl)-4-{2-[(4-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}butyl)sulfonyl]ethyl}-1,3-thiazole

[01105] To a solution of the compound prepared in Reference Example 60 (140mg) in DCM (1.5mL) was added mCPBA (60mg). The mixture was stirred at 20℃ for 16h to give a colorless solution. Then mCPBA (60mg) was added and the mixture was stirred at 20℃ for 3h to give a white suspension. The mixture was washed with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica column (PE to 24% EtOAc in PE) to give the title compound (104mg).

[01106] LCMS: retention time 1.116 min, (Method A); MS (ESI, Pos.): m/z 476.2 $[M+H]^+$.

[01107] Reference Example 62: 4-({2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethyl}sulfonyl)-1-butanol

[01108] To a mixture of the compound prepared in Reference Example 61 (104mg) in THF (2mL) was added 1M TBAF in THF (0.44mL). The reaction was stirred at 20℃ for 16h to give a yellow mixture. The mixture was concentrated in vacuum. The residue was purified by silica gel column (DCM to 6% MeOH in DCM) to give the title compound (60mg).

[01109] LCMS: retention time 0.812 min, (Method A); MS (ESI, Pos.): m/z 362.0 $[M+H]^+$.

[01110] Example 167: (3S,4R,5R,6S)-1-[4-({2-[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]ethyl}sulfonyl)butyl]-3,4,5,6-azepanetetrol

[01111] Example 167 was synthesized according to procedures analogous to Reference Example 7 and Example 69 using the compound prepared in Reference Example 62 instead of the compound prepared in Reference Example 6.

[01112] LCMS: retention time 1.467 min, (Method B); MS (ESI, Pos.): m/z 507.1 (M+H)+;

[01113] ^{1}H NMR (CD_3OD) δ: 7.63-7.58, 7.49, 7.15-7.04, 3.65-3.56, 3.47-3.35, 3.17-3.08, 2.94-2.81, 2.62, 1.92-1.84, 1.71-1.61.

[01114] Reference Example 63: 2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]-2-propanol

[01115] To a mixture of ethyl 2-(4-fluorophenyl)thiazole-4-carboxylate (CAS No. 132089-35-1, 0.50g) in THF (10mL) was added MeMgBr (2.7mL) at 0℃. The reaction was stirred at 20℃ for 16h under N_2 to give a brown mixture. The reaction mixture was quenched by sat. NH_4Claq. and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuum. The residue was purified by flash column with silica gel (PE to 40% EtOAc in PE) to give the title compound (0.45g).

[01116] TLC R_f=0.50 (PE/ EtOAc =3/1).

[01117] Reference Example 64: 4-{2-[(6-bromohexyl)oxy]-2-propanyl}-2-(4-fluorophenyl)-1,3-thiazole

[01118] To a solution of the compound prepared in Reference Example 63 (150mg) in DMF (2mL) was added NaH (51mg) and 1,6-dibromohexane (CAS No. 629-03-8, 0.29mL). The mixture was stirred at 60℃ for 16h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column with silica gel (EtOAc in PE from 5% to 10%) to give the title compound (120mg).

[01119] ^{1}H NMR ($CDCl_3$) δ: 7.90-7.86, 7.07-7.02, 3.32-3.22, 1.85 – 1.75, 1.55, 1.54-1.36.

[01120] Example 168: (3S,4R,5R,6S)-1-[6-({2-[2-(4-fluorophenyl)-1,3-thiazol-4-yl]-2-propanyl}oxy)hexyl]-3,4,5,6-azepanetetrol

[01121] Example 168 was synthesized according to procedures analogous to Example 1 using the compound prepared in Reference Example 64 instead of the compound prepared in Reference Example 1.

[01122] LCMS: retention time 0.724 min, (Method A); MS (ESI, Pos.): m/z 483.1 (M+H)+;

[01123] ^{1}H NMR (CD_3OD) δ: 8.00, 7.37, 7.22, 3.57, 3.42-3.36, 3.31-3.28, 2.78, 2.59-2.41, 1.63, 1.58-1.49, 1.48-1.40, 1.39-1.31, 1.30-1.21.

[01124] Reference Example 65: {[7-(2-biphenylylmethoxy)-5-heptyn-1-yl]oxy}(triisopropyl)silane

[01125] Titled compound was synthesized according to procedures analogous to Reference Example 6 using ((triisopropylsilyl)oxy)hept-5-yn-7-ol (CAS No. 1802596-80-0) and 1-(bromomethyl)-2-phenylbenzene (CAS No. 19853-09-9).

[01126] TLC Rf=0.75 (PE/EtOAc=5/1).

[01127] Example 169: (3S,4R,5R,6S)-1-[7-(2-biphenylylmethoxy)-5-heptyn-1-yl]-3,4,5,6-azepanetetrol hydrochloride (1:1)

[01128] Titled compound was synthesized according to procedures analogous to Reference Example 15, 16 and Example 69 using the compound prepared in Reference Example 65 instead of the compound prepared in Reference Example 14.

[01129] LCMS: retention time 0.733 min, (Method A); MS (ESI, Pos.): m/z 440.2 (M+H)+;

[01130] ^{1}H NMR (CD_3OD) δ:7.53-7.48, 7.46-7.40, 7.40-7.34, 7.31-7.25, 4.45, 4.16-4.01, 3.83, 3.60-3.56, 3.45-3.32, 3.27-3.13, 2.33-2.20, 1.95-1.73, 1.58-1.47.

[01131] Example 170 and 171

[01132] Example 170 and 171 were synthesized according to procedures analogous to Reference Example 21, 22, 15, 16, Example 71 and 72 using [2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methanol instead of [5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methanol.

[01133] Example 170: (3S,4R,5R,6S)-1-[(5R)-6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol hydrochloride (1:1) (isomer 1)

[01134] LCMS: retention time 0.792 min, (Method A); MS (ESI, Pos.): m/z 491.3 (M+H)+;

[01135] ^{1}H NMR (DMSO-D_6) δ:9.39, 7.76, 7.64, 7.41, 4.86-4.61, 3.96-3.84, 3.76-3.53, 3.34, 3.28-3.20, 3.16-3.03, 1.82-1.54, 1.47-1.28;

[01136] SFC Retention Time: 4.121min (Method: A3).

[01137] Example 171: (3S,4R,5R,6S)-1-[(5S)-6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol hydrochloride (1:1) (isomer 2)

[01138] LCMS: retention time 0.694 min, (Method A); MS (ESI, Pos.): m/z 491.3 (M+H)+;

[01139] ^{1}H NMR (DMSO-D_6) δ: 9.57, 7.76, 7.68-7.59, 7.41, 4.82-4.60, 4.66, 3.98-3.83, 3.75-3.56, 3.34, 3.29-2.96, 1.83-1.2;

[01140] SFC Retention Time: 4.535min (Method: A3).

[01141] Example 172 to 174

[01142] Example 172 to 174 were synthesized according to procedures analogous to Reference Example 1 and Example 1 using the corresponding alcohol compound instead of (4-methylphenyl)methanol.

[01143] Example 172: (3S,4R,5R,6S)-1-{6-[(3-ethoxy-4-fluorobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[01144] LCMS: retention time 0.681 min, (Method A); MS (ESI, Pos.): m/z 416.1 (M+H)+;

[01145] ^{1}H NMR (CD_3OD) δ: 7.11-7.00, 6.92-6.82, 4.44, 4.10, 3.59, 3.48, 3.45-3.31, 2.90-2.76, 2.54, 1.66-1.48, 1.45-1.24.

[01146] Example 173: (3S,4R,5R,6S)-1-{6-[(4-chlorobenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol

[01147] LCMS: retention time 0.683 min, (Method A); MS (ESI, Pos.): m/z 388.1 (M+H)+;

[01148] ^{1}H NMR (CD_3OD) δ: 7.33, 4.47, 3.70-3.43, 3.39, 2.86–2.74, 2.61-2.43, 1.71-1.44, 1.41-1.27.

[01149] Example 174: (3S,4R,5R,6S)-1-(6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol hydrochloride (1:1)

[01150] LCMS: retention time 0.689 min, (Method A); MS (ESI, Pos.): m/z 493.1 (M+Na)+;

[01151] ^{1}H NMR (CD_3OD) δ: 7.44-7.28, 7.22, 4.54, 4.17-4.03, 3.84, 3.63-3.56, 3.42-3.33, 3.22-3.04, 2.54, 1.83-1.62, 1.51-1.37.

[01152] Pharmacological Experimental Example 1: Evaluation of human GBA1 enzyme inhibitory activity

[01153] The inhibitory activity was determined using recombinant GBA enzyme and 4-methylumbelliferyl-β-D-glucopyranoside (4-MUG) as a substrate in 384-well format. The reaction was carried out in the acidic assay buffer (pH5.2 Mcllvaine buffer, 0.25% sodium taurocholate, and 0.1% Triton X-100). 5μL of 4x test compound solution was preincubated with the 10μL of GBA enzyme (0.1ng/μL) at RT for 5min. The reaction was initiated by adding 5μL of 2mmol/L substrate solution followed by incubation at 37℃ for 60min. The reaction was stopped by addition of an equal volume of stop solution (1mol/L glycine solution adjusted to pH10 using 1mol/L NaOH) which raised the pH for optimal fluorescence intensity. The released 4-methylumbelliferone (4-MU) was measured (excitation 355nm, emission 450nm) on fluorescence spectrophotometer. The blank includes GBA followed by sequential addition of stop solution and substrate. The inhibitory activity (IC_{50} value) of a test compound was calculated from the inhibition rate of 4-MU production at each compound concentration,

with the average of the blank group as 100% inhibition and the average of the compound non-treated group as 0% inhibition.

[01154] From the above pharmacological experiments, it was found that the compound of the present disclosure had GBA1 inhibitory activity. For example, the IC_{50} values of some compounds of the present disclosure are shown in Table 1 below. These data suggest that the compound of the present disclosure may be able to bind GBA1 and stabilize the GBA1 to such an extent that it is able to protect it from degradation.

[01155] Pharmacological Experimental Example 2: Evaluation of human GCS enzyme inhibitory activity

[01156] The lysate of HL60 cells were used in this assay. HL60 cells were thawed and cultured in RPMI1640 medium with 10% FBS. The cells were passaged once before use. The cells were collected to a centrifuge tube and washed three times with PBS, then the number of the cells was counted. The M-PER (R) Mammalian Protein Extraction Reagent containing protease cocktail inhibitor (1:100) was added to the cells at 1mL/4x10^7 cells, and the mixture was kept on ice for 30min while being mixed every 5min to lysis the cells. The cell lysate was sonicated for 15min in ice-water bath, and centrifuged at 1000rpm for 10min at 4℃. The supernatant was collected and the protein concentration was determined using BCA assay. The supernatant was aliquoted and stored at -80℃ as the enzyme source. Twenty-five nanoliters of 1000x test compound was dispensed to the 384-well assay plate by ECHO. The reaction cocktail (100mmol/L Tris buffer (pH7.5) containing 10μmol/L NBD-C6 ceramide, 25μmol/L UDP-glucose, 35μmol/L dioleoylphosphatidylcholine, 1mmol/L dithiothreitol, and 1mmol/L EGTA) was prepared and dispensed at 15μL to each well. The reaction was initiated by adding 10μL of cell lysate (1mg/mL) to the well. The plate was kept 37℃ for 90min and the reaction was terminated by adding 75μL of stop solution (methanol:acetonitrile (6:5) containing 200ng/mL tolbutamide as internal control). The reaction solution was vortexed and centrifuged to obtain the supernatant for further LC/MSMS analysis. The reaction product, NBD-C6-glucosylceramide, was analyzed using AB Sciex triple quadrupole mass spectrometer. The inhibitory activity (IC_{50} value) of a test compound was calculated from the inhibition rate of NBD-C6-glucosylceramide production at each compound concentration, with the average of the blank group as 100% inhibition and the average of the compound non-treated group as 0% inhibition.

[01157] From the above pharmacological experiments, it was found that the compound of the present disclosure had potent GCS inhibitory activity. For example, the IC_{50} values of some compounds of the present disclosure are shown in Table 1 below.

[01158] Pharmacological Experimental Example 3: Evaluation of human GBA2 enzyme inhibitory activity

[01159] The human GBA2 plasmid was prepared as follows. The complete open reading frames for GBA2 (human NM_020944.2) was amplified from human tissue, using specific primers containing restriction sites and an extended Kozak sequence in front of the start codon. PCR products was subsequently cloned in the pGEM-T vector, and their sequence was verified. The appropriate fragment was subcloned in pCDNA-3.1 using the added restriction sites. HEK293T cells were transiently transfected with the human GBA2 plasmid using Lipo3000 reagents. The transfected cells were homogenaized in 4 volumes of ice-cold 25mM potassium phosphate (pH5.5) followed by sonication for 3x1 min and centrifuged for 1h at 100,000×*g*. The supernatant was discarded and the pellet was resuspended and centrifuged again. The membrane pellet was resuspended in ice-cold 25mM potassium phosphate (pH5.5) which was used as crude enzyme in the following enzymatic assay.

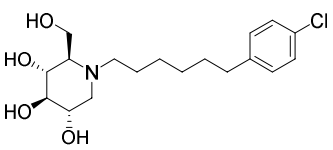
[01160] The inhibitory activity was determined using the GBA2-rich membrane suspensions prepared as above and 4-MUG as a substrate in 384-well format. The reaction was carrierd out in the assay buffer (pH5.2 Mcilvaine buffer, 0.25% sodium taurocholate, and 0.1% Triton X-100). 10μg of enzyme suspension was preincubated at 4℃ for 30min with 1mmol/L Conduritol B Epoxide (CBE) to inhibit GBA1. The reaction was initiated by adding 0.5mmol/L (final concentraion) substrate solution, followed by incubation at 37℃ for 45min. The reaction was stopped by addition of stop solution (400mmol/L glycine solution adjusted to pH10.6 using 1mol/L NaOH). The released 4-methylumbelliferone was measured (excitation 362nm, emission 450nm) on fluorescence spectrophotometer. The inhibitory activity (IC_{50} value) of a test compound was calculated from the inhibition rate of 4-MU production at each compound concentration, with the average of the blank group as 100% inhibition and the average of the compound non-treated group as 0% inhibition.

[01161] From the above pharmacological experiments, it was found that the compound of the present disclosure did not have potent GBA2 inhibitory activity. The compound of the present disclosure was found to be a compound with less concern for the accumulation of glycolipid by GBA2 inhibition. For example, the IC_{50} values of some compounds of the present disclosure are shown in Table 1 below.

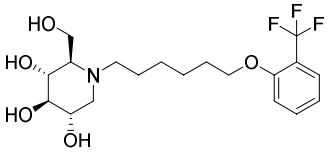
[01162] [Table 1]

Example	GBA1 inhibition IC_{50} (μM)	GCS inhibition IC_{50} (μM)	GBA2 inhibition IC_{50} (μM)
1	5.1	2.0	>10
21	2.4	0.06	>10
72	1.2	0.19	>10
74	1.7	0.03	>10
101	1.1	0.17	>10
107	1.2	0.13	>10
135	3.2	0.67	>10
139	5.1	0.22	>10

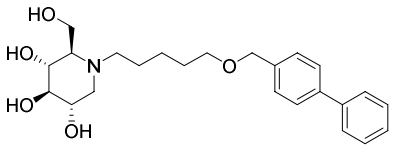
[01163] Using the compound described in UV6.2 (Comparative compound A), or UV6.8 (Comparative compound B) in Patent Document 1, or the Compound 3 (Comparative compound C) described in Patent Document 2 as comparative compounds, the inhibitory activities of GBA1, GCS, and GBA2 were measured. The IC_{50} values of comparative compounds are shown in Table 1-1 below.



Comparative compound A



Comparative compound B



Comparative compound C

[01164] [Table 1-1]

Comparative compound	GBA1 inhibition IC_{50} (μM)	GCS inhibition IC_{50} (μM)	GBA2 inhibition IC_{50} (μM)
A	0.08	0.91	0.001
B	0.04	1.20	0.002
C	0.28	0.01	0.001

[01165] From the above results, it was found that the compound of the present disclosure has less GBA2 inhibitory activity than comparative compounds.

[01166] Pharmacological Experimental Example 4: Evaluation of human GBA1 cellular activity

[01167] The Gaucher's cell line with β-glucocerebrosidase mutation of N307S (Coriell Institute, Cat. GM00372) was cultured and expanded using EMEM with 15% FBS. The cell was passaged at least twice and could be used until the 20th passages. The cells were seeded at the density of $1.25x10^4$ cells/well in 96-well plate. After cell culturing overnight, 50μL of

cell medium was discarded, and 50μL of the diluted compound was added (with 0.3% DMSO). The cells were treated with compound for 6days. On day 6, the cells were washed once with HBSS and incubated in HBSS for 3h followed by lysing using 30μL assay buffer (pH5.2 Mcllvaine buffer supplemented with 0.25% sodium taurocholate, 0.5% Triton X-100 and protease cocktail inhibitor) for 5min at 4℃ on shaker. For GBA enzymatic assay, 15μL of cell lysate was incubated with 5μL of 4-MUG (6mmol/L) for 60min in 384 well format followed by adding 20μL of stop solution (1mmol/L glycine solution adjusted to pH10 using 1mol/L NaOH). The reaction product of 4-MU was measured (excitation 355nm, emission 450nm) on fluorescence spectrophotometer. For the protein quantification, 4μL of cell lysate was mixed with 36μL of Pierce BCA reagents for 30min. The protein was detected according to the manufacturer's instructions. Enzyme activity in cell lysate was normalized to protein concentration. The blank included substrate and assay buffer followed by addition of stop solution. Enzyme activity in cells treated with DMSO was used as a negative control, and results were represented as the percent change in enzyme activity in cells treated with each compound. For example, the percent change in enzyme activity in cells are shown in Table 2 below.

[01168] From the above pharmacological experiments, it was found that the compound of the present disclosure had potent GBA1 chaperone activity.

[01169] [Table 2]

Example	Percent change in enzyme activity at test concentration				
	0.12μM	0.37μM	1.1μM	3.3μM	10μM
1	155	166	200	221	230
72	160	214	248	259	284
74	96	150	185	193	216
100	142	147	145	163	169
101	157	157	209	219	227
107	109	110	141	157	199
135	102	108	127	153	191
139	115	119	154	157	204

[01170] Pharmacological Experimental Example 5: Evaluation of sphingolipids lowering activity

[01171] The Gaucher's cell line with β-glucocerebrosidase mutation of N307S (Coriell Institute, Cat. GM00372) will be cultured and expanded using EMEM with 15% FBS. The cell will be passaged at least twice once thawed. The cells were seeded at cell density of

$1x10^5$ cells/dish in 6cm dish. After cell culturing overnight, the cell medium will be discarded and 4mL of test compound solution will be added (with 0.1% DMSO). The cells will be treated with compound for 6days. On day 6, the cells will be washed twice with PBS. Then, 1mL of 20mmol/L acetic acid in ethanol will be added to the dish and the cells will be collected using Cell scraper. This step will be repeated to obtain 2mL of cell extracts. Ten microliters of internal standard (β-GlcCer d18:1/17:0 (200ng/mL), β-GalSPB d18:1 (d_5) (200ng/mL), and β-LacCer d18:1/17:0 (200ng/mL), Cer d18:1/17:0 (200ng/mL) will be added to it and the mixture will be vortexed, followed by addition of 1mL of chloroform. The mixture will be sonicated for 10min on ice and vortexed again, then centrifugated at 4℃ for 3min at 2,130×g . The supernatant will be collected and dried up by centrifugal concentrator. The dried sample will be dissolved by 0.2mL of chloroform /Methanol (2:1, v/v) and the level of sphingolipids will be measured by SFC/MS/MS.

[01172] Pharmacological Experimental Example 6: Evaluation of cognitive impairment in mice.

[01173] Evaluating the pharmacological activity of a test compound include improvement of cognitive impairment in mice. For example, improvement of cognitive impairment by a compound may be evaluated by using the following method.

[01174] Mice (16 to 23-month old male C57BL/6 mice (Charles River Laboratories Japan, Inc.)) are used. A test compound and its vehicle are orally administered once daily for 2weeks. After that, the cognitive function will be assessed by the novel object recognition (NOR) test using a plastic box (460mm * 300mm * 450mm) with a video camera as the experimental apparatus. The evaluation is performed in a dark room and the light intensity is adjusted to approximately 20lux near the experimental apparatus. To acclimatize animals to the evaluation environment, the mice are moved to the evaluation room at least 1hour prior to the start of the trial. The study will be conducted over 3days. For acclimation to the experimental apparatus on Day 1, the mice are placed in a cage and allowed to move freely for 10minutes. This step is performed twice at 4h intervals. In the acquisition trial on Day 2, two identical objects (familiar objects) are placed on the cage and performed in the same way for 10minutes. The two objects are placed apart on a line parallel to the long side of one cage. The distance between the object and the inner wall of the two adjacent surfaces is 10cm. In the test trial on Day 3, one of the objects used in the acquisition trial is replaced by a novel object with a different color and shape, and the animals behave in the same manner for 10minutes. The test trials start 24hours (Acceptable range: 23 to 25hours) after the acquisition

trials. From the video images recorded in the test trials, the exploration time for each object is measured. From the exploration time of familiar and novel objects, the total exploration time and the novel object recognition rate are calculated by the following equation.

[01175] Total exploration time (seconds) = Exploration Time for familiar object + Exploration time for novel object

[01176] Recognition index (%) = 100 * (Exploration time for novel object / Total exploration time)

[01177] [Formulation Examples]

[01178] Formulation Examples

[01179] The following components are mixed by an ordinary method and compressed to obtain about 10,000 tablets containing 10 mg of the active ingredient in one tablet.

[01180] ●(3S,4R,5R,6S)-1-{6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol..... 100 g

[01181] ●Carboxymethylcellulose calcium (disintegrant)..... 20 g

[01182] ●Magnesium stearate (lubricant)..... 10 g

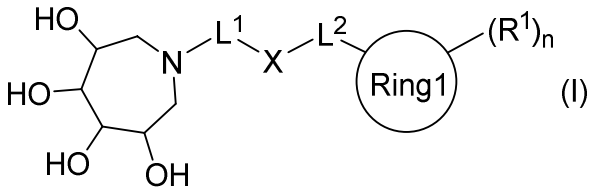
[01183] ●Microcrystalline cellulose..... 870 g

[01184] [Industrial Applicability]

[01185] The compound of the present disclosure has GBA1 and GCS dual modulatory activity, and thus a drug containing the compound of the present disclosure as an active ingredient is useful as an agent for preventing and/or treating a disease associated with GBA1 and/or GCS.

Claims

[Claim 1] A compound represented by formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

L^1 represents (1) a C4-7 alkylene, (2) a C4-7 alkenylene, or (3) a C4-7 alkynylene,

L^1 may be substituted with one to five R^{L1}s,

R^{L1} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, or (10) a hydroxyl group,

a plurality of R^{L1}s may be the same or different,

L^2 represents (1) a C1-3 alkylene, (2) a C2-3 alkenylene or (3) a C2-3 alkynylene,

L^2 may be substituted with one to four R^{L2}s,

R^{L2} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, or (10) a hydroxyl group,

a plurality of R^{L2}s may be the same or different,

X represents (1) a bond, (2) -O-, (3) -S-, (4) -SO-, or (5) $-SO_2-$,

Ring 1 represents (1) a benzene ring (2) a naphthalene ring or (3) a 5- to 10-membered heterocyclyl,

R^1 represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group, (4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, (10) a C5-7 carbocyclyl, (11) a 5- to 7-membered heterocyclyl, (12) -O-(C5-7 carbocyclyl), or (13) -O-(5- to 7-membered heterocyclyl),

a plurality of R^1s may be the same or different,

the groups (2) to (13) in R^1 may be substituted with one to five R^{1-1}s,

R^{1-1} represents (1) a halogen atom, (2) a C1-6 alkyl group, (3) a C2-6 alkenyl group,

(4) a C2-6 alkynyl group, (5) a C1-6 alkoxy group, (6) a C1-6 haloalkyl group, (7) a C2-6 haloalkenyl group, (8) a C2-6 haloalkynyl group, (9) a C1-6 haloalkoxy group, (10) a C1-6 alkyl sulfonyl group, (11) a cyano group, or (12) a phenyl group,

a plurality of R^{1-1}s may be the same or different,

the symbol:



represents that a substituent is bonded to the α-configuration, β-configuration or a mixture of α- and β-configurations at an appropriate ratio, and

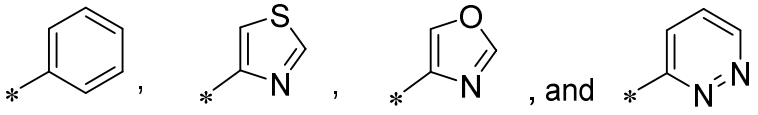
n represents an integer of 0 to 5.

[Claim 2] The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein L^1 represents a hexylene group.

[Claim 3] The compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein X represents -O-.

[Claim 4] The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein L^2 represents a methylene group.

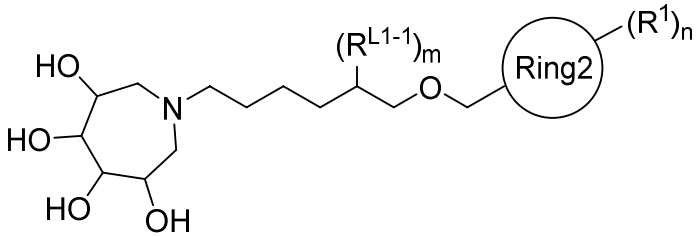
[Claim 5] The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein Ring 1 represents a ring structure selected from the group consisting of the following ring structures;



wherein the * mark represents a bonding position with L^2.

[Claim 6] The compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein R^{L1} represents (1) a halogen atom, or (2) a C1-6 alkyl group.

[Claim 7] The compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein the compound represented by formula (I) is a compound represented by formula (I-1):



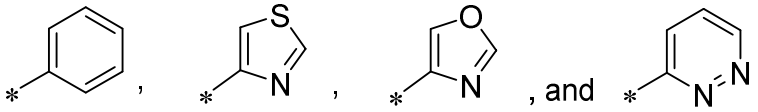
(I-1)

wherein R^{L1-1} represents (1) a halogen atom, or (2) a C1-6 alkyl group,

a plurality of R^{L1-1}s may be the same or different,

m represents an integer of 1 to 2,

Ring 2 represents a ring structure selected from the group consisting of the following ring structures;



wherein the * mark represents a bonding position with methylene, and

other symbols represent the same meaning as the symbols described in claim 1.

[Claim 8] The compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein the compound represented by formula (I) is a compound selected from the group consisting of:

(1) (3S,4R,5R,6S)-1-{6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol,

(2) (3S,4R,5R,6S)-1-(6-{[2-(3,5-difluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl)-3,4,5,6-azepanetetrol,

(3) (3S,4R,5R,6S)-1-{(5R)-6-[(3-ethoxy-4-fluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

(4) (3S,4R,5R,6S)-1-{(5S)-6-[(3-ethoxy-4-fluorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

(5) (3S,4R,5R,6S)-1-[(5R)-5-fluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol,

(6) (3S,4R,5R,6S)-1-[(5S)-5-fluoro-6-{[2-(4-fluorophenyl)-1,3-thiazol-4-yl]methoxy}hexyl]-3,4,5,6-azepanetetrol,

(7) (3S,4R,5R,6S)-1-[(5R)-6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol,

(8) (3S,4R,5R,6S)-1-[(5S)-6-{[5-(3,5-difluorophenyl)-2-methyl-1,3-oxazol-4-yl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol,

(9) (3S,4R,5R,6S)-1-{(5S)-6-[(4-ethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

(10) (3S,4R,5R,6S)-1-{(5R)-6-[(4-ethylbenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

(11) (3S,4R,5R,6S)-1-{(5S)-6-[(4-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

(12) (3S,4R,5R,6S)-1-{(5R)-6-[(4-chlorobenzyl)oxy]-5-fluorohexyl}-3,4,5,6-azepanetetrol,

(13) (3S,4R,5R,6S)-1-{(5S)-5-fluoro-6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol,

(14) (3S,4R,5R,6S)-1-{(5R)-5-fluoro-6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol,

(15) (3S,4R,5R,6S)-1-[(5S)-6-{[6-(3,5-difluorophenyl)-3-pyridazinyl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol, and

(16) (3S,4R,5R,6S)-1-[(5R)-6-{[6-(3,5-difluorophenyl)-3-pyridazinyl]methoxy}-5-fluorohexyl]-3,4,5,6-azepanetetrol.

[Claim 9] A compound (3S,4R,5R,6S)-1-{6-[(4-methylbenzyl)oxy]hexyl}-3,4,5,6-azepanetetrol, or a pharmaceutically acceptable salt thereof.

[Claim 10] A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 as an active ingredient, and a pharmaceutically acceptable carrier.

[Claim 11] The pharmaceutical composition according to claim 10, which is a GBA1 chaperone modulator.

[Claim 12] The pharmaceutical composition according to claim 10, which is a GCS inhibitor.

[Claim 13] The pharmaceutical composition according to claim 10, which is a GBA1 and GCS dual modulator.

[Claim 14] Use of the compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, or the pharmaceutical composition according to any one of claims 10 to 13, in the manufacture of a medicament for treating and/or preventing a disease associated with GBA1 and/or GCS.

[Claim 15] The use according to claim 14, wherein the disease associated with GBA1 and/or GCS is selected from the group consisting of Parkinson's disease, Lewy body disease, Gaucher disease, Multiple system atrophy, Fabry disease, Niemann-Pick disease type C, lysosomal storage diseases, Dementia, epilepsy, bipolar disorder, schizophrenia, anxiety disorder, major depression disorder, Sandhoff's disease, Tay-Sachs disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, cognitive impairment, learning disabilities, gait disorders, sleeping disorder, neurological disorders, CNS disorders, polycystic kidney disease, type 2 diabetes, cancer, open angle glaucoma, endometriosis, multiple myeloma, virus infection, inflammation,

systemic lupus erythematosus, hepatitis, Guillain-Barre Syndrome, diabetic nephropathy, and skin disorder.

[Claim 16] The use according to claim 14, wherein the disease associated with GBA1 and/or GCS is selected from the group consisting of Parkinson's disease, Lewy body disease, and Gaucher disease.

[Claim 17] The use according to any one of claims 14 to 16, wherein the compound, the pharmaceutically acceptable salt thereof, or the pharmaceutical composition is to be administered in combination with one or more agent(s) selected from the group consisting of levodopa, carbidopa, pramipexole, ropinirole, rotigotine, apomorphine, zonisamide, droxidopa, cabergoline, pergolide, tolcapone, entacapone, selegiline, rasagiline, safinamide, istradefylline, foslevodopa/foscarbidopa, benserazide, bromocriptine, talipexole, amantadine, trihexyphenidyl, biperiden, donepezil hydrochloride, imiglucerase, velaglucerase alfa, eliglustat, alglucerase, and miglustat.

[Claim 18] The compound or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, or the pharmaceutical composition according to any one of claims 10 to 13, for use in therapy.